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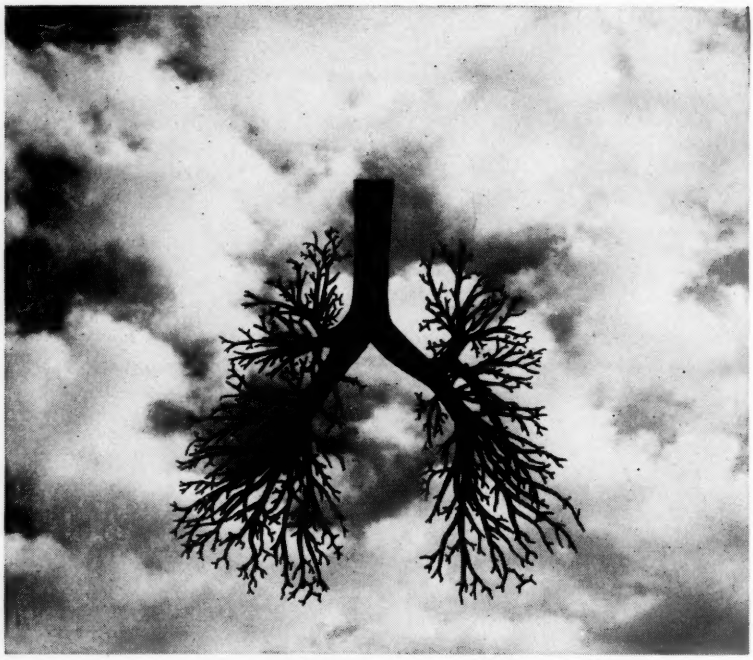

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TREATMENT OF EMPHYSEMA BY ARTIFICIAL PNEUMOPERITONEUM

ANDREW L. BANYAI, M.D.

Milwaukee, Wisconsin

EMPHYSEMA is the most frequent and most serious complication of bronchial asthma. If the pessimistic attitude of the medical profession is taken as an index of prognosis of emphysema, any new departure of therapeutic promise should be given due consideration. Inasmuch as current clinical experience supports the claim that suitable corrective, though not curative, measures are available, a review, or perhaps a revision, of precepts pertaining to the management of this disease is in order. With this premise, it is proposed to assay the pathogenesis and pathomechanics of emphysema, with particular reference to bronchial asthma.

Two types of emphysema are observed in bronchial asthma: (1) acute, transient, (2) chronic, permanent. If it is recognized that bronchospasm is one of the cardinal manifestations of bronchial asthma, it may be postulated that asthmatic paroxysms are always associated with emphysema. The latter results from partial bronchial occlusion of the check-valve type which permits the ingress of air to alveoli distal to the site of stricture but prevents its egress. In this manner the trapping of some of the air inhaled results in a retrograde stretching of the alveoli. The condition which develops in connection with trapping of air in this fashion may well be designated as alveolar pneumatic hypertension.

While it is admitted that bronchospasm in itself may be sufficient to bring about alveolar pneumatic hypertension, there is no doubt that in most instances of bronchial asthma concurrent events characteristic of this

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disease contribute their share to narrowing of the bronchial lumen of this type. These changes include thickening of the hyaline basement membrane of the bronchial mucosa, its leukocytic and eosinophilic infiltration, together with infolding of the thickened mucosa and with profuse outpouring of mucus from the dilated and distended glands. The gradually developing hypertrophy of the peribronchial smooth muscles implies greater likelihood for spastic occlusion. It is of interest that small peripheral bronchi, the walls of which contain less cartilaginous elements, are provided with a rich supply of smooth muscles. The muscle thickness is 0.2 mm in a bronchus of 10 mm diameter, while it is 0.1 mm in bronchioles 1 mm in diameter, that is, five times as strong in the latter as in the former.

The question may be raised whether or not normal air current is prone to enter groups of alveoli beyond the site of partial bronchial occlusion. Is this a physical impossibility? Air currents are subject to the same physical laws as water currents. They move from a site of higher pressure toward areas of lower pressure. Ordinarily, no additional air could pass into the alveoli during inspiration after the pressure of their air content equals that of the atmosphere. However, during asthmatic paroxysms, as the result of diminished entry of air into the alveoli, hypoxia of the blood stimulates the respiratory center. This stimulation is followed by greater inspiratory effort on the part of the diaphragm and chest wall muscles. In consequence of his, the intrapleural pressure becomes more negative. Increased negativity of the intrapleural pressure is transmitted to the alveoli and here, through its steeper inflow gradient (suction effect), favors the entry of additional air.

With the cessation of asthmatic attacks, occlusive bronchial changes may completely disappear. This is followed by the escape of air entrapped in the distended alveoli. Transitory or reversible as this form of emphysema may be, it is far from being benign or innocuous. Frequent recurrence of asthmatic paroxysms as well as status asthmaticus lead to undue, sustained distention of the alveoli, with all of its potential deleterious consequences which culminate in chronic, pseudohypertrophic emphysema.

There are two other potent factors instrumental in the development of emphysema as a sequel to allergic bronchial asthma, namely, chronic infection of the lower air passages and the aerodynamic trauma of frequent, strenous cough. Chronic lung infection may lead to destructive changes in the supportive and myoelastic elements of the lung either by direct toxic influences or by associated perivascular fibrosis. The latter causes obstruction or complete obliteration of some of the nutritional blood vessels, with consequent diminished blood flow and untoward effect upon the implicated lung structure. In chronic pulmonary infections there is a tendency to reflex bronchospasm.

The deleterious effect of excessive intrapulmonary pressure during severe coughing can be readily appreciated. During the compressive phase

of cough (deep inspiration followed by closure of the glottis and by a forced expiratory effort) the intrapulmonary pressure may stand as high as from 80 to 200 mm of mercury over and above atmospheric pressure. The possible stretching and damaging effect (aerodynamic trauma) of such high intrapulmonary pressure may be expressed in units of weight. It represents an increase of from one-tenth to more than one-fourth of atmospheric pressure, that is, from 1.5 to 3.75 pounds per square inch.

The term pseudohypertrophic emphysema portrays the essence of the disease under discussion more descriptively than the conventional designation as hypertrophic emphysema. Hypertrophy signifies an increase in the specific elements of an organ or muscle. In this type of emphysema there is neither an increase in the number of functionally competent alveoli nor a proportionate augmentation of the number, size, and functional capacity of corresponding capillary vessels.

Chronic pseudohypertrophic emphysema of the lung is characterized by the following pathologic changes:

1. Destruction of the peribronchial and peribronchiolar elastic fibers.

2. Dilatation or rupture of the alveoli, with consequent formation of large air spaces. When the latter is localized subpleurally, they are designated as subpleural blebs. The ones localized in other parts of the lung parenchyma are referred to as bullae. It is reasonable to assume that the seemingly haphazard topography of these air cysts is the result of irreversible bronchostenotic changes in diverse parts of the lung. Bronchostenosis of this sort is brought about by the combined effect of localized infection, bronchospasm and accumulation of exudate.

3. Destruction of some of the capillaires of the lesser circulation, which coincides with the disappearance of normal alveolar architecture.

4. Increase in the size of the lung. This is due partly to the presence of cysts of pneumatic hypertension and partly to the passive adaptation of the lung to the thoracic cage.

5. Distention of the thoracic cage. This is attributable to two causes: a. the formation of air cysts of increased pressure; b. the outward pull of the inspiratory muscles of the chest wall. When, as the result of loss of elastic elements of the lung, its centripetal (hilusward) contractility is greatly reduced, there is a proportionate decrease in or complete disappearance of the negativity of the intrapleural pressure. The inspiratory muscles of the chest wall, not being obliged to counteract the inward pull of the intrapleural negative pressure, are bound to distend the thoracic cage.

6. Abnormally low position of the diaphragm. This is brought about mainly by the disappearance of the upward traction of the intrapleural negative pressure. In its abnormally low position the diaphragm is functionally handicapped or completely defunctionalized. Consequently, its respiratory motions are slight, absent, or may be paradoxical, rising on inspiration and descending on expiration.

Ventilatory derangement of the lung resulting from dysfunction of the diaphragm is aggravated by distention of the chest wall. Inspiratory muscles attached to the chest wall are unable to cause further dilatation of the thoracic cage or, at the most, their function in this respect is far below par. Consequently, the accessory respiratory muscles come into play.

Circulatory disturbances in emphysema result from the following causes:

1. The return flow of venous blood to the right auricle of the heart is decreased because of the lessened negativity of the intrathoracic pressure.

2. Diminished or absent distention of the lung on inspiration implies a lack of dilatation of the pulmonary vascular bed. Thus the normal gradient, which facilitates blood flow from the right ventricle to the lung, is absent.

3. There is a significant decrease in pulmonary circulation because of destruction of perialveolar capillaries and, also, because of compression of capillaries and small blood vessels by distended air cysts.

A number of measures have been advocated for the treatment of pseudo-hypertrophic emphysema. These include: (1) expiratory pressure breathing with pursed lips; (2) inhalation of gradually increased concentrations of oxygen; (3) manual compression of the lower anterior parts of the chest, the upper part of the abdomen or both, rhythmically at intervals corresponding to the expiratory phase of the respiratory cycle; (4) breathing exercises; (5) abdominal supports; (6) prolonged recumbency in slightly slanted, head-down position; (7) intermittent positive pressure breathing of oxygen; (8) intermittent positive-negative pressure breathing; (9) administration of 2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide (Diamox®, Lederle), an inhibitor of the enzyme, carbonic anhydrase; (10) surgical intervention (resection of lung cysts, resection of the pulmonary plexus).

It is beyond the purpose of this presentation to discuss these items in detail. Rather, I wish to offer an assaying of artificial pneumoperitoneum, a method which I have been using for the treatment of emphysema for nearly twenty-five years. The benefits derived from this procedure are attributable to the following factors.

1. Artificial pneumoperitoneum elevates the diaphragm and thereby refunctionalizes this previously defuntionalized muscle. The resulting improved respiratory excursions are comparable to restoration of function after reduction of a dislocated joint. Normal diaphragmatic movements are predicated upon a gradient which exists between the thoracic cage with its negative pressure and the abdominal cavity with its predominantly atmospheric pressure. Artificial pneumoperitoneum is instrumental in

establishing such a gradient by its positive pressure, contrasted to the nearly atmospheric pressure in the pleural space encountered in pronounced emphysema.

2. Pneumoperitoneum may decompress some of the large air cysts and thus decrease their interference with the ventilatory and respiratory function of intact alveoli and capillaries. Also, elevation of the diaphragm reduces the size of the lung. Consequently, the amount of residual air, which dilutes and vitiates the tidal air, is diminished.

3. Under the influence of artificial pneumoperitoneum, the intrapleural pressure becomes more negative. This greater negativity draws the diaphragm upward and the chest wall inward. In consequence of the latter, the inspiratory muscles of the chest wall are likely to regain some of their normal function and thus increase respiratory excursions of the chest wall.

4. With the improved function of the respiratory muscles, including the diaphragm, a more even and widespread distribution of the inhaled air is made possible. Better oxygenation of the blood is brought about.

5. Improved respiratory function of the thorax together with the increased negativity of the intrapleural pressure facilitate the venous return from the periphery of the greater circulation to the heart and the flow of blood from the right ventricle to the lung.

Technically, pneumoperitoneum is a simple and safe procedure that can be carried out by a physician of average manual dexterity. With the exception of bedridden patients who are to be hospitalized prior to the initial treatment, pneumoperitoneum may be induced in the office or at a clinic. For the initial treatment, I prefer the site three fingerbreadths below and to the left of the umbilicus, but any other location on the anterior abdominal wall is suitable, provided scars of surgical incision are avoided. The patient is in the supine position on the operating table. Surgical asepsis is mandatory. Sterile drapes are applied. It is good practice to use local anesthesia (1 per cent procaine) and thoroughly infiltrate the abdominal wall at the site of entry for each treatment. A 19-gauge, 2½-inch needle is used for the injection of air. A three-way stopcock is attached to it. The needle is connected to a standard "pneumo" apparatus before insertion. The needle is pressed slowly and gently through the abdominal wall perpendicular to the skin surface. As it passes through the tissues gradually, one can feel the resistance offered by the layers of the abdominal wall. When one feels that the point of the needle has reached the abdominal cavity, it is mandatory to apply a 5 or 10 cc syringe to the upper aperture of the three-way stopcock, and switch the valve so that the needle and syringe are connected. By drawing back on the piston of the syringe, it is possible to ascertain that the point of the needle is not in a blood vessel. When no blood is withdrawn by this maneuver, 25 cc of air are injected from the "pneumo" apparatus. The flow of air may be

permitted by force of gravity or it may be introduced under low positive pressure. If the point of the needle is not in the peritoneal cavity but in the abdominal wall, the flow of air is very slow and after the injection of 25 cc the manometer attached to the "pneumo" apparatus will show a non-oscillating positive pressure of 12 to 24 cm of water. If such is the case, the needle should be slowly advanced and the aforementioned maneuver is repeated. When the point of the needle is in the free peritoneal space, following the injection of 25 cc of air, the intraperitoneal pressure registered on the manometer of the apparatus is less than 10 cm. of water.

At the time of the initial treatment, as well as for "refills," I have found it expedient to inject air into the peritoneal cavity by small increments. After the injection of 50 cc of air, manometer reading is taken so as to be certain of the proper location of the point of the needle and also for avoiding unduly high intraperitoneal pressure. To prevent air embolism, it is mandatory to draw back on the piston of the syringe connected to the needle PRIOR TO THE INJECTION OF EACH 50 CC OF AIR. The amount of air given with the first treatment is from 500 to 600 cc. "Refills" are given at weekly intervals, using 400 to 800 cc of air. The exact amount is decided on fluoroscopic examination, depending upon the position and mobility of the diaphragm one desires to attain, before each treatment. It is unwise to give larger amounts of air because they are bound to cause limitation in motion of the diaphragm, and, thus, the treatment defeats its own purpose. Wearing a snugly fitting abdominal support, night and day, adds to the efficacy of this treatment. It is a good policy to tell the patient about the likelihood of shoulder pain following the first treatment. This is only of few hours duration and can be relieved easily by having the patient in the supine position or by the administration of ordinary analgesics. Artificial pneumoperitoneum is well tolerated by the patient and it may be continued for years. Pertinent technical details have been described in the author's previous publications.

Artificial pneumoperitoneum is a corrective, not a curative, measure in the management of emphysema. While it cannot restore destroyed alveoli and elastic fibers of the lung, it is capable of ameliorating pulmonary function. Its therapeutic benefits, physically as well as psychologically, become manifest as soon as adequate pneumoperitoneum is established.

It is well to keep in mind that artificial pneumoperitoneum has its *a priori* limitations. Failures may be attributable to the following causes: (1) anatomically and functionally irreversible, extensive loss of alveoli and elastic elements of the lung; (2) widespread pulmonary fibrosis; (3) sustained bronchospasm; (4) diaphragmatic adhesions which prevent its elevation; (5) atrophy of disuse of the diaphragm in long standing emphysema; (6) heart failure which cannot be corrected; and (7) uncontrollable complications which interfere with cardio-respiratory function.

CONCLUSIONS

1. Assaying the pathogenesis and pathomechanics of pseudohypertrophic emphysema points toward the feasibility of using therapeutic measures for its management which aim at the correction of the deranged ventilatory and respiratory functions of the lung.

2. Experience has shown that, in spite of its innate limitations, artificial pneumoperitoneum is a useful procedure in the treatment of this disease.

3. Therapeutic benefits derived from artificial pneumoperitoneum do not absolve the physician of the responsibility of treating the underlying bronchial asthma adequately, with special regard to hyposensitization, removal of exposure to antigens, avoidance of trigger factors, administration of bronchorelaxant drugs and the use of other adjunct measures of value.

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SECOND INTERNATIONAL CONGRESS OF ALLERGOLOGY

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THE MANAGEMENT OF THE ALLERGIC PATIENT DURING PREGNANCY

ANGELO L. MAIETTA, M.D., F.A.C.A.
Boston, Massachusetts

THE MANAGEMENT of the pregnant allergic patient presents a challenge to the attending physician. It is a barbed challenge replete with therapeutic pitfalls and dangers strewn all along the way from early pregnancy through childbirth. Yet, during the past thirty years, only a very few papers discussing this subject or one of its several facets have appeared in the literature. It is the purpose of this paper to present the therapeutic problems of sixteen allergic female patients who have been treated for allergic rhinitis, hay fever and bronchial asthma during their pregnancies.

A DIAGNOSTIC PROBLEM

The appearance of solitary, subclinical or atypical asthmatic symptoms early in pregnancy may not be recognized as allergic manifestations because they may not fit the textbook picture of bronchial asthma. The intractable, nonproductive cough, the smothered feeling, the inability to breathe properly, the easy dyspnea and diaphragmatic pain are symptoms of bronchial asthma which are sometimes incorrectly explained purely on a mechanical basis. The following case illustrates such a diagnostic problem.

I. M., a twenty-four-year-old woman with a negative family history of allergy, had eczema in infancy and morning sneezing spells during adolescence.

Shortly after her first conception, which occurred at age twenty-four, she developed a nonproductive cough, more distressing during the night, which did not respond to codeine or ammonium chloride. She thought that the cough medication produced nausea and itching of the skin, but was told that nausea was due to the pregnancy. She was unable to sit on a low divan or overstuffed chair without developing a cough, diaphragmatic pain in the upper quadrants and a smothered feeling associated with an inspiratory wheeze and distress rather than expiratory difficulty.

She repeatedly stated that she was unable to get sufficient air into her lungs. These episodes were explained as due to the upward pressure of the enlarged uterus against her lungs. Repeated x-rays of the chest were negative. She was told that she did not have tuberculosis, cancer, tumor, abscess or infection of the lung, and no foreign bodies were visible.

At the sixth month she accepted a submucous resection to improve her breathing. Despite this surgical procedure, her asthmatic symptoms, still unrecognized, became progressively worse. She was treated with morphine or codeine and was assured

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Dr. Maietta is Chief of the Allergy Clinic, Carney Hospital.
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that her symptoms would disappear after delivery. During these months, she had consulted, in addition to her obstetrician, with an internist on several occasions, a cardiologist and two otolaryngologists.

Finally, shortly before term, during one of her severe nocturnal seizures, she was given an injection of epinephrine instead of the customary morphine and within a few minutes her symptoms dramatically disappeared. With the establishment of bronchial asthma as the diagnosis, the condition was readily controlled with palliative antiallergic therapy, and her asthma was traced to a kapok mattress. She delivered a normal full-term baby without any ill effects.

Since this episode, she has had another full-term pregnancy throughout which her asthma was satisfactorily controlled.

In retrospect, the mismanagement of this case hinges upon two pertinent facts which did not receive proper evaluation. It is essential to recognize that the component symptoms of bronchial asthma may appear singly at first and, as time passes, will merge with each other to produce the textbook picture of bronchial asthma. Diagnostic confusion can be avoided by recognizing that inspiratory wheezing and inability to draw in sufficient air instead of the classic expiratory difficulty oftentimes is presented as the chief complaint by a patient with bronchial asthma. Obviously, inspiratory volume is reduced because of the large quantity of air already trapped within the lung.

SYSTEMIC REACTIONS

Constitutional reactions following pollen desensitizing injections may appear with dramatic suddenness and can be serious. In the female patient, such systemic reactions may involve the uterus.[1,3,4] The following case of uterine bleeding occurring on four different occasions at the height of a constitutional reaction illustrates the involvement of the uterus as a shock organ.

S. W., a white woman, aged thirty-two, married and the mother of two children, is exquisitely sensitive to ragweed pollen and has received ragweed hyposensitizing injections for hay fever and pollen asthma for the past few years. Although local reactions were small, constitutional reactions occurred in July, 1949, following a dose of 1500 PU of ragweed extract, in July, 1950, with 1800 PU, April, 1953, with 900 PU and August, 1953, with 1500 PU.

The symptoms included generalized pruritus, urticaria, coryza, asthma and uterine bleeding. Suitable medication controlled the systemic reaction, but the vaginal flow continued for several hours thereafter necessitating the use of three to four vaginal pads. These metrorrhagic episodes did not disturb the normal menstrual cycle; the next regular period occurred on schedule.

Involvement of the pregnant uterus as a shock organ has led to abortion.[2] Such an eventuality, though fortunately rare, is always a distinct possibility and demands that extreme caution be exercised in the management of the pregnant allergic patient.

TABLE I. POLLEN CASES

Case	Age	Primi-para	Multi-para	Symptoms	Preseasonal Therapy	Coseasonal Therapy	Top Pollen Dose
1 S. W.	28		3	hay fever, pollen asthma	1st and 2nd trimesters		900 PU ragweed
2 B. L.	30		3	hay fever, pollen asthma	1st and 2nd trimesters		2000 PU ragweed
3 L. B.	35	x		hay fever	1st and 2nd trimesters		2000 PU ragweed
4 F. L.	35		2	hay fever, pollen asthma	2nd trimester ragweed	2nd trimester grass	50 PU grass 2000 PU ragweed
5 M. M	34		3	hay fever, pollen asthma		2nd trimester ragweed	50 PU ragweed
6 E. L.	32		2	hay fever, pollen asthma	1st trimester		2000 PU ragweed
7 A. M.	40		3	hay fever, pollen asthma	1st trimester ragweed	1st trimester grass	50 PU grass 2000 PU ragweed
8 N. E.	29		2	hay fever, pollen asthma	1st trimester grass 1st and 2nd trimesters ragweed		2000 PU grass 2000 PU ragweed
9 F. C.	31	x		hay fever	1st and 2nd trimesters		2000 PU ragweed
10 J. P.	30	x		hay fever	1st trimester		2000 PU ragweed
11 M. C.	33		2	hay fever	2nd trimester ragweed	2nd trimester grass	50 PU grass 2000 PU ragweed

SPECIFIC DESENSITIZATION

The keynote in the specific treatment of the expectant mother is conservative therapy because of the danger of a constitutional reaction that may involve the uterus and thereby interrupt pregnancy. Considering the medicolegal situation that may evolve after such an eventuality, it behooves the allergist to proceed slowly and with great caution. Patients are prone to blame the injections for any untoward effect, and a miscarriage, under such circumstances, will be viewed by them with considerable suspicion. Nevertheless, assurance can be given that pregnancy is not a contraindication for conservative specific desensitization. Indeed, in the more severe clinical cases, where the severity of the allergic symptoms themselves could be a cause for a miscarriage, conservative specific desensitization is the treatment of choice. Each pregnant patient should be considered separately and her antiallergic treatment individualized to fit her needs. In setting up such a specific desensitization program, the following factors must be considered.

Since constitutional reactions must be avoided during pregnancy, it is safe to proceed with an underdose program. Diminutive doses may not give a very good result but, at least, they will reduce the severity of the symptoms.

In pollen cases especially (Table I), a diminutive dose program administered preseasonally coupled with a suitable antihistaminic orally if needed during the season has given satisfactory results. The following pollen doses comprised the underdose schedule: 20, 50, 100, 200, 300, 450, 600, 900, 1200, 1500, 1800 and 2000 PU. The injections were administered

TABLE II. DUST AND VACCINE CASES

Case	Age	Primi-para	Multi-para	Symptoms	Treatment During
12 I. M.	24		2	asthma	1st and 2nd trimesters
13 E. C.	35		2	asthma	1st and 2nd trimesters
14 M. C.	22	x		asthma	1st and 2nd trimesters
15 T. O.	28	x		allergic rhinitis	3rd trimester
16 E. C.	31		3	allergic rhinitis, asthma	1st and 2nd trimesters

weekly or biweekly depending upon the amount of time available for preseasonal treatment. From 5 to 10 mg of Chlorprophenpyridamine maleate (Chlor-Trimeton Maleate® 100 mg/cc) was added to each injection to preclude further the possibility of a constitutional reaction.

The only exception to this schedule was the patient described above. In April, 1953, she had a constitutional reaction involving the uterus with uterine bleeding following a 900 PU dose. During her most recent pregnancy (1954), because of this experience, her preseasonal pollen doses were deliberately kept smaller than those suggested in the diminutive dose schedule. Her top preseasonal pollen dose was 900 PU. Clinically, she had a satisfactory season.

The twelve doses enumerated in the diminutive schedule when administered weekly consume one trimester of pregnancy; given biweekly two trimesters. Thus, when the specific season occurs during the third trimester, the hyposensitizing injections can be given biweekly preseasonally during the first and second trimesters; when the season occurs during the second trimester, the specific injections can be given weekly preseasonally during the first trimester. This diminutive dose schedule with a top pollen dose of 2000 PU has given satisfactory results. Whenever mild symptoms occurred during the season, they were promptly controlled with a Chlorprophenpyridamine Maleate 8 mg repeat tablet.

Coseasonal symptoms occurring during any trimester were treated with six small coseasonal doses (5, 10, 20, 30, 40, 50 PU) and an 8 mg repeat tablet of Chlorprophenpyridamine every eight hours as needed. The injections were combined with 5 to 10 mg of Chlorprophenpyridamine Maleate (100 mg/ cc) and were administered semiweekly. The results were satisfactory but not as good as those obtained with preseasonal therapy. Cortisone or ACTH were not used for fear of disturbing the hormone balance.

Specific treatment was deferred in patients who were scheduled for confinement two to four weeks before the onset of their season. These cases, not included in this paper, received rapid preseasonal desensitization after delivery.

Patients requiring dust extract or bacterial antigens (Table II) also

received them in diminutive doses. The increments were kept small. The injections were administered weekly, biweekly or monthly as required. Specific injections were given up to the third trimester and resumed again after delivery. Palliative medication (ephedrine, aminophylline, KI) was employed as needed. The results were satisfactory. A dust-sensitive patient presenting herself for initial therapy during the third trimester was treated with small doses of dust extract (dilution 1:400,000 through 1:40,000) and kept comfortable with suitable palliative medication until after delivery, when a more intensive antiallergic regimen was instituted.

Previous specific therapy and the age of the expectant mother merit consideration. Expectant mothers with a known top pollen dose and pollen schedule are not much cause for concern especially if they are young and multiparous. In contrast, an elderly primipara with a long-awaited pregnancy and without a known top pollen dose is cause for more concern, not only because of the obstetric difficulties that may attend such a person, but also because an abortion or miscarriage inadvertently caused by a constitutional reaction may produce irreparable psychic trauma. Judicious, conservative management of these patients is of paramount importance.

PSYCHOLOGICAL ASPECT

Pregnancy is a major event in the life of a woman. It assumes even more important significance when the expectant mother is an active allergic patient. Fearful lest active symptoms disrupt her pregnancy or that pregnancy should aggravate her allergic complex, the expectant mother is in a state of anxiety. Anxiety is the most important factor in pregnancy[5] and may increase out of proportion the central fear of pregnancy which is the fear of death. Anxiety and tension aggravate the allergic state. In such cases, emotional preparation for pregnancy and delivery should be integrated with antiallergic therapy.

Assurance for the safety of the mother and child was cheerfully given. The expectant mother was assured that there was close co-operation with her obstetrician and that intelligent, antiallergic management would keep her asymptomatic or, in the event of a flare-up, would quickly control her symptoms and thus reduce to a minimum the risk of miscarriage due to stress and strain of severe allergic symptoms. She was made to understand that during her hospital confinement her allergy, properly controlled, would have no bearing upon the outcome of the delivery; that allergic environmental control could be carried out more easily and that suitable palliative medication would be quickly administered as needed by the nursing staff.

PARTURITION STAGE

Allergic patients with a known drug allergy should give this information to their obstetrician who obviously will be cautious in their use. Aspirin,

barbiturates, codeine or morphine, alone or in combination with other drugs, are commonly employed to decrease pain the early stages of labor. They are also common offenders. When a sensitivity to these drugs exists and their administration is imperative, they should be given combined with 5 to 10 mg of Chlorprophenpyridamine Maleate (100 mg/cc).

Penicillin is still a favorite antibiotic. During labor or the puerperium it may be given prophylactically to ward off a flare-up of a quiescent infection. When required in a known penicillin-sensitive patient, it should be administered in combination with a suitable anthistaminic.

Vital information concerning existing drug sensitivity and the general condition of the allergic patient should be given to the anesthetist. Whenever practical, the anesthetist should visit the patient prior to delivery or obstetric procedure in order to obtain a satisfactory history, perform a physical examination and allay any fears that the patient may have concerning delivery or operation.

The more commonly employed anesthetic agents are safe to administer. Nitrous oxide, ethylene and cyclopropane are agents which cause little or no irritation to the respiratory mucosa and are advisable for light anesthesia during a quick perineal delivery provided the patient is well oxygenated. Ether whiffs for a light anesthesia during the perineal stage are contraindicated because ether irritates the membranes and increases mucosal secretions. However, when deeper anesthesia is required, ether is not contraindicated. Sodium pentothal can be used for a fast manipulative procedure. Spinal or deep general anesthesia are recommended for extensive surgical procedures. Sensitivity to novocaine may preclude spinal anesthesia. Curare is frequently used in conjunction with general anesthetic agents in order to produce greater muscular relaxation. Curare liberates histaminic substances from the body tissues and, for this reason, should be administered slowly. A suitable antihistamine given prior to the administration of curare may be advisable.

When in the course of an obstetric procedure a blood transfusion is indicated in an allergic patient, the addition of 10 to 20 mg of Chlorprophenpyridamine Maleate (100 mg/cc) to the transfused blood is advisable. An antihistaminic preparation could also be given orally prior to the transfusion. If, despite this precaution, an allergic transfusion reaction should occur, the transfusion should be discontinued immediately and epinephrine and antihistamines administered in proper doses as needed.

SUMMARY AND CONCLUSIONS

Diagnostic confusion can be avoided by recognizing that the component symptoms of bronchial asthma may appear singly at first and later merge with each other to produce the textbook picture of bronchial asthma.

The human uterus can be involved as a shock organ in a constitutional

reaction. Uterine bleeding may follow the injection of ragweed pollen extract as a component symptom of a systemic reaction.

The keynote in the specific treatment of the expectant mother is conservative therapy because of the danger of a constitutional reaction that may involve the uterus and thereby interrupt pregnancy. Diminutive pollen doses combined with an antihistamine are recommended.

The allergic expectant mother may be fearful lest her allergic symptoms disrupt pregnancy or the pregnancy aggravate her allergy. These emotional reactions should be understood and treated continuously with cheerful assurance. Emotional preparation for pregnancy and delivery should be integrated with antiallergic therapy.

During parturition and confinement, sedatives, narcotics and antibiotics are employed. When sensitivity to any of these preparations exists and their administration is imperative, they should be given combined with an antihistaminic agent. The more commonly employed anesthetic agents are safe to administer. Blood transfusion reactions should be avoided.

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The office of the ANNALS OF ALLERGY has learned of a technical research assistant, experienced in biochemical research, who desires to relocate. She has worked on blood coagulation, steroid hormones, carbohydrate metabolism, and food analysis, and is familiar with handling radioisotopes. Any organization in need of such a technician may be placed in contact with her through the office of the Managing Editor of the ANNALS OF ALLERGY, 401 Marquette Bank Building, Minneapolis 2, Minnesota.

ALLERGY AND HEADACHES

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ALLERGY is an important factor in the etiologic diagnosis of headaches. It is the single cause of some types of headaches and an important factor in others. Allergists should not be afraid to tackle the headache problem, keeping their own specialty in its proper place. Internists, otolaryngologists and psychiatrists should likewise keep the allergic factor in mind, even in vascular headaches such as migraine.

TABLE I. MECHANISMS OF INTRACRANIAL PAIN
(Adapted from Wolff[35])

MECHANISM	CLINICAL CAUSES
1. TRACTION on veins passing to venous sinuses from brain surface; DISPLACEMENT of sinuses.	Swelling of brain. Displacement by tumor. Low intracranial pressure. Air in subarachnoid space.
2. TRACTION on middle meningeal arteries.	Tumors of or pressing on dura.
3. TRACTION on large basal arteries, their main cerebral branches or nearby pia-arachnoid.	Aneurysms or tumors.
4. DISTENTION and DILATATION of intracranial arteries.	Intravenous histamine. Other vasodilators. Fever and sepsis. Common vascular headaches.
5. INFLAMMATION in or about any pain-sensitive structure in the head.	Meningitis. Subarachnoid hemorrhage. Meningeal tumor invasion.
6. DIRECT PRESSURE on nerves containing pain-conducting fibers.	Tumors.

Wolff[35] and his associates have shown that there are only a few pain-sensitive structures within the skull. "Of the intracranial structures, the great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries, and the cerebral arteries at the base of the brain are sensitive to pain. The cranium (including the diploic and emissary veins), the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles, and the choroid plexuses are not sensitive to pain."

Wolff also lists six mechanisms of pain, as shown in Table I. To these must be added the pain caused by alteration of cerebrospinal fluid pressure. Early literature assumed that pain accompanied increased intracranial pressure. Wolff and others have shown experimentally that the contrary is also true: pain accompanies decreased cerebrospinal pressure.

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TABLE II. INCIDENCE OF CERTAIN TYPES OF HEADACHE
(From a study of 4,634 individuals (cross-section population) by Ogden[25])

Frontal headache	47.1%
Occipital headache	10.1
Migraine (broadly defined)	8.6
Migraine (rigidly defined)	3.3
Histaminic cephalalgia	0.1

TABLE III. SYMPTOMS REFERABLE TO ALLERGY IN STUDY OF 4,634 INDIVIDUALS
(64.8 per cent with headaches. From Ogden[42])

	HEADACHE GROUP	NO HEADACHE GROUP
No nasal symptoms	55.1%	81.2%
No colds	7.8	23.4
No chest or throat symptoms	72.1	86.4
Allergy in family	25.1	11.3

These mechanisms apply only to intracranial pain. There are also headaches associated with disease of other structures without the cranium. These include the eyes, ears, paranasal sinuses, throat, teeth, cervical spine and musculature enclosing the head. Some of these must be considered in discussing the pain associated with allergic and vascular headaches.

There have been many attempts at classification of headache, based upon site, mechanism, etiology and periodicity. Allergic headaches, which are the only ones we shall discuss here, fall into three groups: (1) headaches associated with frank nasal allergy; (2) so-called "allergic headaches," which are primarily frontal, but occasionally occipital; (3) vascular headaches, including migraine. The incidence of these headaches is shown in Table II, while Table III demonstrates the association of headaches in general with allergic symptoms. Table IV shows the many factors which enter into the causation of headaches, according to the patient (and patients are not always wrong). These may be primary or important secondary factors.

The most common type of truly allergic headache is that associated with nasal allergy. This duplicates the so-called "sinus headache" which can occur as a result of chronic or severe acute sinus or nasal disease. This brings up an important point for all physicians interested in treatment of headaches: all types of allergic headaches can be duplicated by other diseases—and vice versa.

The old literature on "sinus headache" emphasized three possible mechanisms: (1) The lining mucosa of the sinuses becomes so swollen as to meet the mucosa of the opposite side, obliterating the sinus cavity or leaving a slit-like aperture; (2) occlusion of drainage passage leads to stagnation and increased pressure within the sinuses; (3) "vacuum headache" (Sluder) in the frontal sinus. All of these have been pretty well disproven now, although blockage of drainage passages predisposes to nasal and sinus infection. Hansel[14] in particular has emphasized the importance of super-

TABLE IV. FACTORS SUSPECTED BY PATIENTS AS CAUSES OF HEADACHE
(From Ogden[24])

COMPLAINTS OF PATIENTS	PER CENT OF 3005 PATIENTS
Eye strain	35.1%
Fatigue	32.5
Menstruation	23.8 (31.1% of all women)
Constipation	16.7
Worry	13.5
Colds	12.5
Sinus trouble	11.6
Emotions	10.6
Overheating	6.5
Allergy	4.7
No idea	12.2

TABLE V. SENSITIVITY OF NASAL STRUCTURES TO PAIN
(Stimulus used is that capable of exciting a 1+ pain reaction on the tongue, using a pain scale of 1 to 10+. From Holmes et al[8])

Floor of nose	1+
Septum	1
Turbinates	3-4
Nasal sinus ostia	6-8
Walls of sinuses	1

imposed infection in allergic noses as a cause of increased headache, as well as other symptoms. He has even stated that allergic sinus disease is frequently painless until and unless infection supervenes.

Recent work by Wolff and associates[19] has shown that the prime site of "sinus pain" is the mucous membrane at the ostia of the sinuses. They demonstrated that, in an edematous blocked nose, minor stimuli, such as cold air, can cause typical sinus pain across the bridge of the nose, over the zygoma and over and behind the eyes. Table V shows the relative pain sensitivity of various intranasal structures. The sinuses themselves are relatively insensitive to pain, but allergic or infectious edema of the ostial membranes can cause severe headaches.

Many patients reporting to the allergist or otolaryngologist complain of sinus headaches as one of their main symptoms. The physician must be awake to the allergic factors which so frequently cause these pains. Most patients with hay fever or perennial allergic rhinitis will admit, under direct questioning, that they suffer from headaches associated with these ailments. It is obvious that headache patients, under proper questioning, will frequently reveal nasal symptoms.

There are also some allergic patients who have headaches of a similar type, but deny that the nose is blocked at the time the pain is present. This presents an etiologic enigma which has puzzled several authors. Are these headaches also based upon nasal allergy? Both Eyermann[4] and Ogden[26] have described this syndrome. The headaches are primarily frontal and occur in patients with allergic noses; occipital pains may be associated. Eyermann believed that food allergy was the prime cause, while Ogden blamed it on inhalant allergy, primarily to house dust. Both agreed that

proper allergic treatment will eventually result in cessation of the headaches. Eyermann believed that cerebral edema or hyperemia was the cause of this type of pain, while Ogden favored dilation of the anterior meningeal arteries. Until either of these is proven, localized mucosal edema at the sinus ostia is also a logical mechanism.

Hansel[14] has also described an allergic headache syndrome associated with cerebral and peripheral edema. Polydypsia, peripheral edema and weight gain precede the attack, while polyuria and weight loss herald its end. The pain is generalized, with a sense of pressure, dizziness and mental confusion. It occurs in allergic individuals and is frequently accompanied by other allergic manifestations, such as urticaria, angioedema, atopic dermatitis or gastrointestinal allergy. The entire attack, which lasts from twelve to twenty-four hours, can be reproduced by ingestion of the causative food.

This syndrome links vascular headaches with allergy, particularly food allergy. As will be shown shortly, cerebral edema is a factor in the migraine attack. The above (Hansel) syndrome is a type of vascular headache in which the concurrence of other allergic manifestations makes the etiologic diagnosis simple. In other vascular headaches the allergic factors are less obvious, but still frequently present.

There are many types of vascular headaches described in the literature—far too many. "The folly of expounding a clinical syndrome expressing the pain of every individual branch of the carotid arterial tree must be apparent. This is particularly true in that all combinations of segmental vascular functional misbehavior occur, and in the same individual over many years the pattern tends to be a shifting one. Hence, one ends with more atypical syndromes than typical. The subject must be taught and dealt with as a vascular imbalance with its expression a vasodilating pain and its locale limited only by the anatomic location of the peripheral branches of the carotid artery. The fog of typical and atypical migraines, histaminic cephalalgias, pseudosinus headache, and atypical neuralgias is thus swept aside and the simple mind can go forward to meet disturbed vascular physiology in whatever locale it may be found."[17]

Because of its clearcut and definite symptomatology and the fact that many well-known physicians have been afflicted by it, migraine is the most widely discussed of the vascular headache syndromes. What is discussed here about migraine should be extended to most other vascular headaches as well.

Migraine is a periodic vascular headache characterized by throbbing, severe, usually unilateral pain accompanied by nausea and photophobia. It is frequently preceded by an aura, most often visual, and can usually be relieved by ergotamine tartrate or DHE 45 if given early enough in adequate doses. Migraine has multiple etiologic factors, including allergy, and is frequently inherited.

None of these features is always present in each migrainous individual. The most constant features we have found, in order of decreasing frequency, are (1) severity; (2) periodicity; (3) nausea; (4) photophobia; (5) unilaterality (at least with some attacks); (6) relief by ergotamine tartrate; (7) throbbing character; and (8) aura. It is not difficult to separate true migraine from nonvascular headaches, provided an adequate history is taken.

Wolff[35] has shown that migraine has three vascular stages. The aura is associated with vasoconstriction; the main head pain is due to vasodilatation; and the prolonged after-pain is associated with edema of the walls of the affected arteries and with muscular spasm. Recently, Hilger[17] has linked these stages through a theory that the main process is the same one throughout: vasoconstriction. There are two mechanisms by which maintained vasoconstriction can lead to eventual vasodilatation: (1) Blood pulsating against a peripheral constricted area causes proximal dilatation (a process similar to that seen with intestinal obstruction); (2) constriction of the vasa vasorum causes edema, transudate formation and flaccidity of the arterial walls. This latter would explain the third stage described by Wolff.

As a corollary of this theory, vasospasm also causes capillary ischemia, which leads to the production of extravascular exudates and edema. Redisch and Pelzer[29] have observed capillary indistinctness during migraine attacks; examinations of the same patients between attacks showed normal capillaries. The same authors noted that intravenous Gynergen® caused the capillaries to become more distinct, albeit transiently.

Goltman[11] demonstrated many years ago that edema is present in migraine, but his observations have largely been ignored. Naffziger has been quoted[16] as stating that, during an attack of migraine, a calcified pineal gland can shift away from the affected side. Pfeiffer et al[28] have linked migraine to a relative decrease in effective blood volume; they and other authors have noted the similarities and frequent coexistence of premenstrual tension and migraine. Klingman[20] produced relief of symptoms in a small group of patients with full doses of ion exchange resins.

Hilger's theory also fits with the work of Harrington and Flocks[16] on ophthalmoplegic migraine, which occurs in some patients with severe, long-standing true migraine. The oculomotor paralysis becomes more severe with each attack, eventually becoming permanent. Previous authors believed that this was due to specific vascular changes in and about the oculomotor nerve. However, Harrington and Flocks showed, in an autopsied case, that there was herniation of the hippocampal gyrus of the brain over the freed edge of the tentorium, pressing on the nerve. They hypothesized that this was due to unilateral cerebral edema.

Many more women have migraine than men; the usual reported ratio (confirmed by our own work) is three or four women to one man. Almost

the same proportion have a family history of migraine. Migraine can begin at a very early age; the majority begin before the age of twenty. Glaser[10] has emphasized that attacks in children are different from those in adults in this ways: (1) Main prodromata are langour, anorexia and abdominal discomfort; (2) Temperature is often elevated (up to 104°); (3)

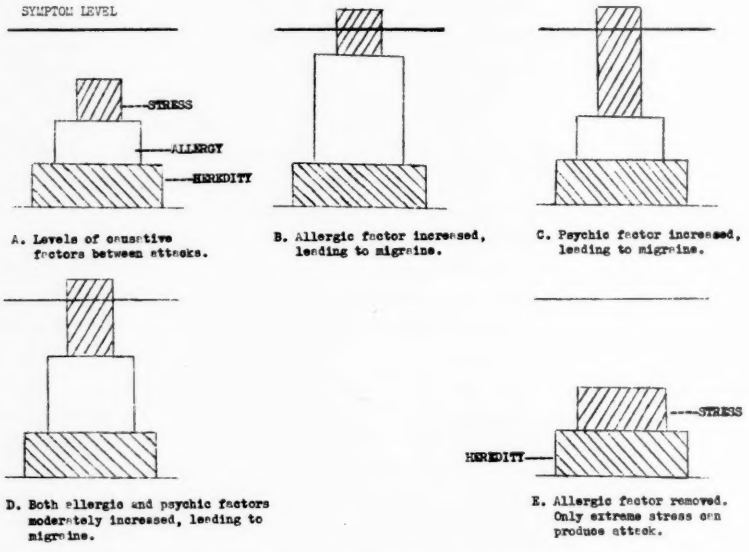

Fig. 1. Relation of allergy and stress in cause of attacks of migraine.

Nausea is more pronounced; (4) Attacks are more frequent, commonly two or three times a week; and (5) Attacks are shorter in duration, usually two or three hours.

The diagnosis of classic migraine is usually not difficult. If it is not clear from the history, true migraine can be reproduced by intravenous histamine. In this test, the migraine appears after cessation of the initial histamine headache, which is due to cerebral vasodilation by the histamine. Other proposed tests include subcutaneous histamine and sublingual nitroglycerine.[27]

Treatment of the attacks is based primarily upon agents which raise the pain threshold or medications which act at the site of the pain. The first group should be restricted to aspirin and drugs similar to APC tablets, since the others of this group are habit-forming. The more specific medicines include primarily ergotamine tartrate, dihydroergotamine and combinations of ergotamine tartrate with caffeine in tablet or suppository form. Many miscellaneous agents have also been tried, ranging from an ice bag on the head to inhalation of 100 per cent oxygen, but none have stood the

test of time. Cortisone has also been used recently, but is not recommended at this time.

"We must recognize . . . that successful treatment is obtained only in eliminating the offending cause. Psychotherapy will hardly help a head-

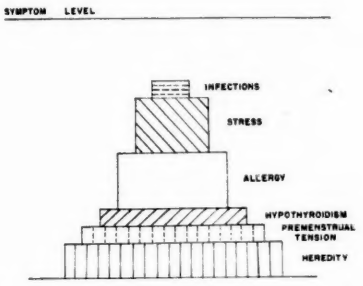

Fig. 2. The interrelationship of some of the multiple factors in the etiology of migraine attacks.

ache originating from an irritated second cervical root, and section of this root will be of questionable aid in headaches of allergic origin."[18]

Migraine is, etiologically, a hydra-headed monster. Within a single patient, there are usually several factors which can, singly or in combination, cause an attack. The interrelationships between these factors are demonstrated in Figures 1 and 2. The main causes, in our experience, are allergy, emotional stress, premenstrual tension, mild hypothyroidism, gastrointestinal upsets and heredity. The association with menses has been discussed previously. Many patients with migraine exhibit a mild hypothyroidism, with a BMR of minus 5 to minus 15. These patients are definitely helped by small doses of thyroid extract, although we have never seen migraine completely relieved by this measure alone. It is merely one of the many facets of the problem. Patients will also frequently state that headache attacks occur in conjunction with minor attacks of intestinal upset, such as the ubiquitous "G.I. flu."

Allergy to foods has, in our experience,[32] been the main precipitating cause of most attacks of migraine. Tables VI and VII demonstrate the food causes and the result of allergic management in our patients. The causes are found through the use of elimination diets, feeding tests and food diaries; skin tests are rarely beneficial. The only major foods which are frequent causes of migraine are chocolate, milk, wheat and pork. Complete elimination of one of these, followed by a feeding test, will usually find the exact cause, although it may take several different food trials to find the right one. Minor food causes are tracked down by food diaries.

Most of the physicians who write about migraine emphasize the emotional causes of attacks, although a few mention allergy as a minor con-

TABLE VI. FOODS KNOWN TO CAUSE MIGRAINE IN FORTY-FIVE PATIENTS
From Unger and Unger[32]

Milk*	15	Fruits	7
Chocolate	13	Apricots	
Wheat	9	Raspberries	
Pork	8	Watermelon	
Other meats	2	Prunes	1 each
Egg	2	Apple	
Fish	2	Citrus fruits	
Shellfish	2	Pears	
Coffee	2	Miscellaneous	9
Vegetables	14	Chicken	
Peanuts	3	Corn	
Onions	2	Root beer	
Celery	2	Molasses	
Potato		Pistachio	1 each
Tomato		Caraway seed	
Soybeans		Garlic	
Peppers	1 each	Sugar (beet, cane, corn)	
Asparagus		Yeast	
Endive		Liquor (?)	2
Broccoli family		Medicines (?)	2

*Patients sensitive to milk are also sensitive to the common forms of chocolate, since they contain milk.

tributory factor. The allergist must point out to these colleagues the ease with which allergy can be investigated while the patient is undergoing the usual battery of diagnostic tests. Elimination diets and food diaries are simple to perform, especially with patients as desperate to find relief as the usual migraine sufferer. The good results they find will surprise these ardent "psychosomaticists."

There has been so much written on the subject of emotions and migraine that the diligent reader ends up thoroughly confused. It is apparent that most of these patients are rigid and perfectionistic, but there is nothing else on which even the majority of authors agree. There has even been an attempt at treating such patients with a rigid regime which includes restriction of sleep to six hours nightly, a rather rigid diet, omission of reading by artificial light and movies, and limitation of physical activities.[9]

"The trouble is that once one starts studying psychosomatic diseases, one can almost always find suspicious emotional situations which occurred before the onset of the disease or just afterward. Psychosomatic, as well as somatopsychic, troubles can easily, for a lazy doctor, become a convenient 'scrapbasket' into which to file permanently all diseases that cannot be accurately diagnosed. He can thus avoid the necessity for physical examination and, of course, side-step all kinds of definitive medications or surgery. Beware!"[5]

One important point rarely discussed in medical literature is that the sufferer from a chronic disease will always, in time, develop emotional tension as a result of that disease. Never is this more true than in the case of migraine. The patient runs from one doctor to another seeking relief, while his friends castigate him for succumbing to "just a headache." By the time

TABLE VII. RESULTS OF ALLERGIC MANAGEMENT IN FIFTY-FIVE PATIENTS WITH MIGRAINE

From Unger and Unger[32]

Complete relief	35 (64%)
Marked improvement (75% or better)	8 (14%)
Moderate Improvement (50-60% better)	2 (4%)
No relief	10 (18%)

he has suffered for five, ten or twenty years, these emotional results of the disease are fully capable of continuing the initial disease. This vicious cycle can be broken by the sympathetic physician who knows what he is doing and can transmit this confidence to the patient. The doctor should have a plan of attack ready to start while the initial workup is proceeding, plus the promise that the regime will help in time. Above all, he must take the time to listen to the patient and to explain what the disease is and how it can be helped. With this as a starting point and a thorough knowledge of medicine and of migraine, many patients can be greatly helped.

A final word about histamine cephalalgia. This is a very rare, but very classic, syndrome characterized by sudden onset of severe burning unilateral pain in and about one eye, accompanied by ipsilateral tearing and rhinorrhea. The pain is so intense that suicide is frequently contemplated.[30] Attacks are short and frequent, up to several times a day; they tend to occur during the night. Those authors who have seen sufficient cases prescribe histamine desensitization as the main preventive treatment. However, Wolff and others believe that histamine cephalalgia is just another variant of vascular headache.

SUMMARY

There are three main types of allergic headaches:

1. In headaches associated with nasal allergy, pain is associated with edema of the nasal mucosa, the site of pain being at or near the sinus ostia.

2. Allergic headaches of a similar type can occur without the nasal blockage; the pain mechanism is unknown at this time.

3. In vascular headaches allergy is an important factor and should always be investigated in such patients. The mechanism of pain is basically vasoconstriction which leads secondarily to vasodilatation and vascular and cerebral edema. Results with allergic management are frequently excellent.

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ATMOSPHERIC POLLEN AND MOLD SPORES IN THE ASHEVILLE AREA

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ASHEVILLE, North Carolina, with the immediately surrounding area, has been known for years as a health resort for persons with diseases of the chest. Although this encompasses chiefly pulmonary tuberculosis, many sufferers have been sent or have come on their own to Asheville or the immediately surrounding mountains for the relief of allergic asthma or hay fever during the pollen seasons, apparently solely on the premise that "a change to the mountains" would bring about relief.

Since there have been no proper atmospheric pollen or mold spore studies done in this area heretofore, and since its reputation as a resort for chest diseases, as well as its mountain location, has attracted many sufferers of asthma and "sinus" complaints and pollen hay fever in the past, an atmospheric survey is considered particularly in order.

METHOD

Pollen counts were done through the three consecutive seasons of 1951, 1952, and 1953. Mold spore counts were made during the pollen seasons of 1952 and 1953. The standard gravity technique was employed using an area of one square centimeter on a twenty-four hour slide, the diary representing the number of pollen grains and mold spores per cubic yard of atmosphere per twenty-four hours.[2] Daily counts were made.

FINDINGS

Pollen

Trees.—The tree pollinating season begins during the middle two weeks of February. Tree pollen was first caught on February 21, both in 1951 and 1952. However, pollen appeared on slides as early as February 3, in 1953. Although in reduced numbers, tree pollen was caught well into June. The height of the tree season, as can be seen in perspective from Figure 1, occurs during the latter half of April and the first half of May. Although the greatest concentration of atmospheric tree pollen is found within this period, both the hickory species and cottonwood are active throughout the months of February and March, particularly the latter.

Oak is the predominant tree pollen in this area and is most active during April and May. Cottonwood, hickory species, beech, ash, and maple follow in approximate order of importance. Tables I, II, III[1] show the

Read by title at the Decennial Congress of the American College of Allergists, April 7-10, 1954, Miami Beach, Florida.

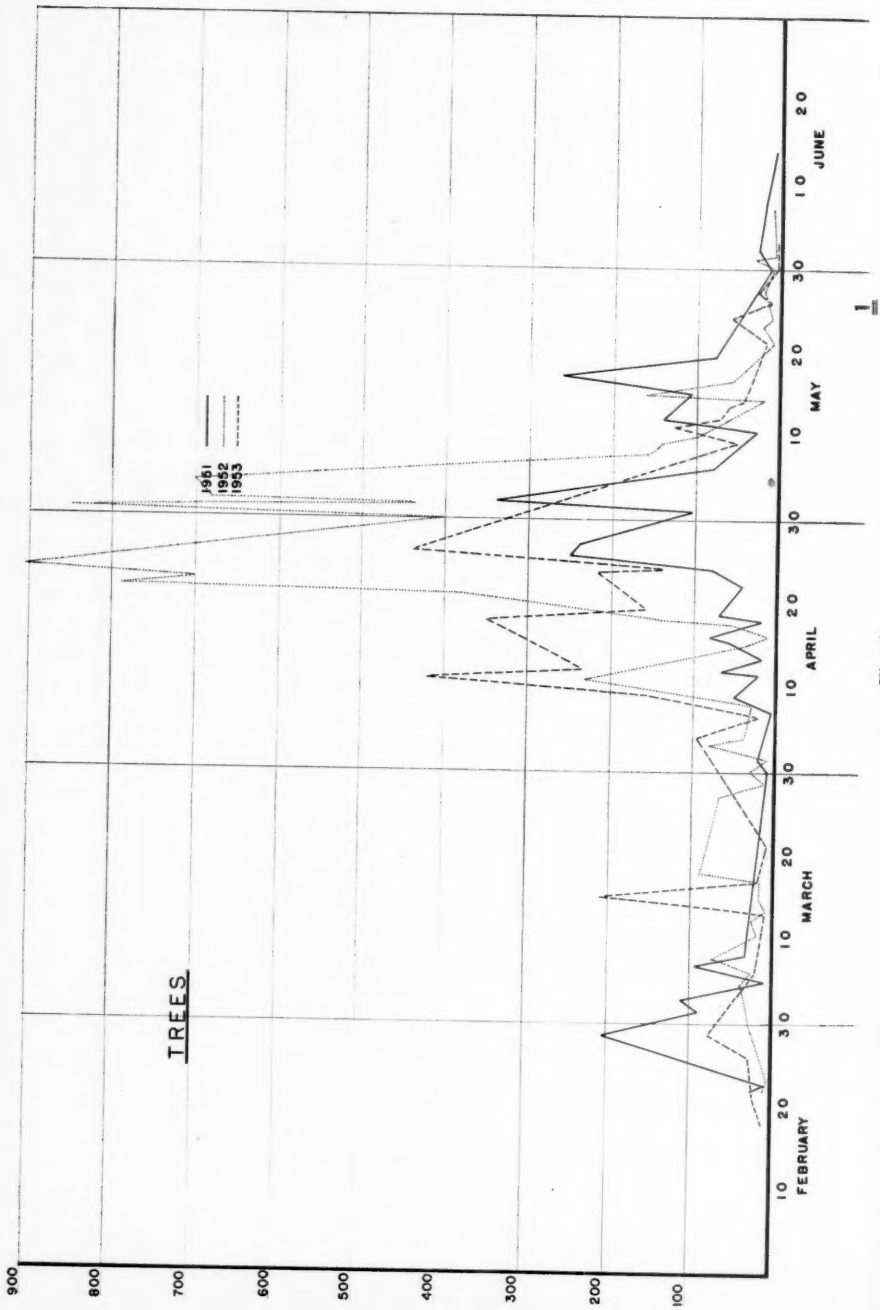

TREES
1951
1952
1953
900
800
700
600
500
400
300
200
100
FEBRUARY
MARCH
APRIL
MAY
JUNE
10
20
30

Fig. 1

POLLEN AND MOLD SPORES—PIPES

TABLE I. TOTAL POLLEN COUNT BY MONTHS, 1951

Pollen	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Total
Alder	27	35	6								68
Elm	7	8		4							19
Maple	6	7	76	31	4						124
Oak	39	6	353	157							555
Hickory Spp.	157	181	24	73	3						438
Ash			108	35							143
Birch	18	1	16	59							94
Cottonwood	111	182	113	48							454
Beech	3		43								46
Sycamore	1	16	33	41							91
Cedar	8		2	4							14
Grass				98	31	37	15				181
E. Plantain				76	82	68	38				264
Chenopod-Amaranth				2	8	3	16	39			68
Ragweed							754	1191	2		1947
Miscellaneous			11			4	27	14			56

TABLE II. TOTAL POLLEN COUNT BY MONTHS, 1952

Pollen	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Total
Alder	11	9	119	45	49						233
Elm	0	0	88	67							155
Maple	2	32	393	139	41						607
Oak	1	94	1925	1777	6						3803
Hickory Spp.	23	128	38	296							485
Ash			233	70							303
Birch		5	117	149							271
Cottonwood	7	259	256								522
Beech	7		433	354							794
Sycamore		10	197	160							367
Cedar			140	211							351
Willow	2	10									12
Grass				289	304	67	25	28			713
E. Plantain				136	286	73	26	5			526
Chenopod-Amaranth				2	16	35	22	146	10		231
Ragweed							282	1852	17		2151
Miscellaneous			13	3		1	8	116	1		142

TABLE III. TOTAL POLLEN COUNT BY MONTHS, 1953

Pollens	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Total
Alder	38	10	13	1							62
Elm	19	13	4								36
Maple	4	15	50	18	7						94
Oak		23	963	80							1066
Walnut)											
Hickory Spp.)	37	12	83	101	11						244
Ash	1	0	78	0	0						79
Birch	14	33	148	12							207
Cottonwood	8	170	138	19							335
Beech		3	278	8							289
Sycamore	1	6	100	4	1						112
Cedar			14								14
Grass				186	118	66	39	36	1		446
E. Plantain				314	263	133	65	11	1		787
Chenopod-Amaranth				2	8	23	166	128	12		339
Ragweed						27	895	1752	64		2738
Miscellaneous				18	1	7	103				129

month during which various pollens were captured for the years 1951, 1952, and 1953, and the number of pollen grains counted for each month with totals for the years.

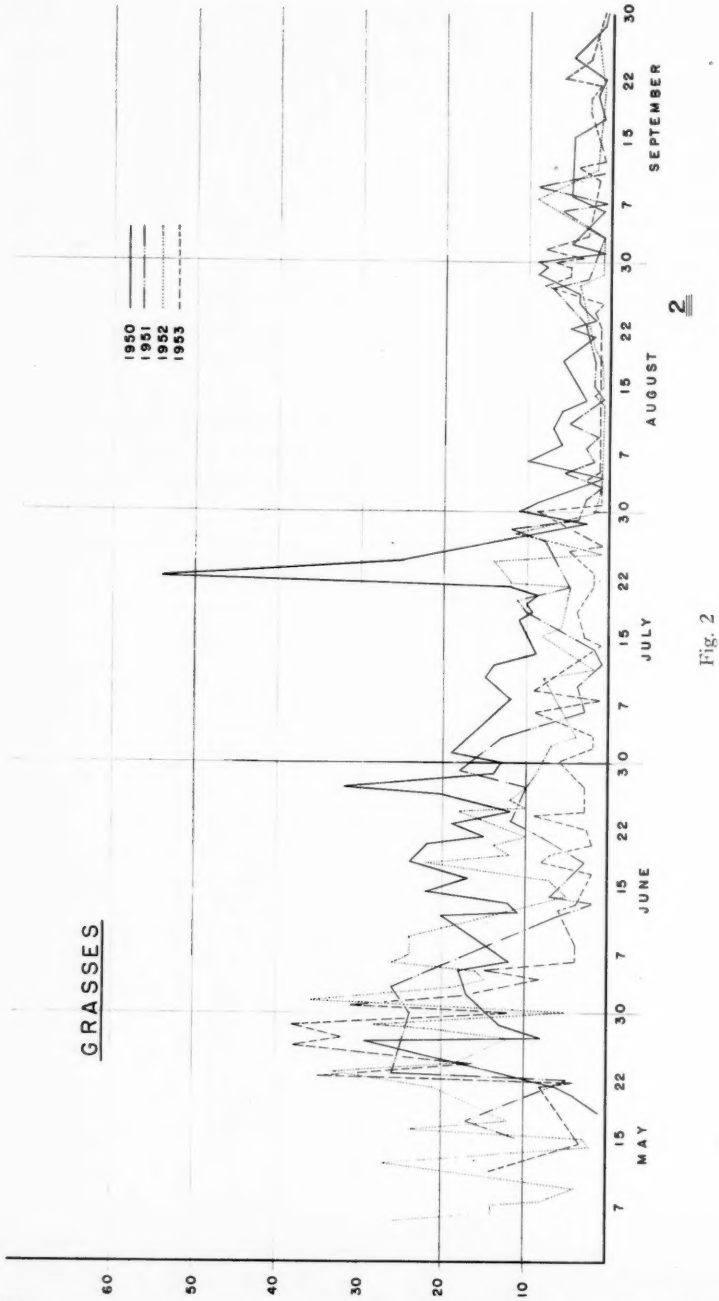

GRASSES
1950
1951
1952
1953
60
50
40
30
20
10
7
15
22
30
MAY
7
15
22
30
JUNE
7
15
22
30
JULY
7
15
22
30
AUGUST
7
15
22
30
SEPTEMBER

Fig. 2

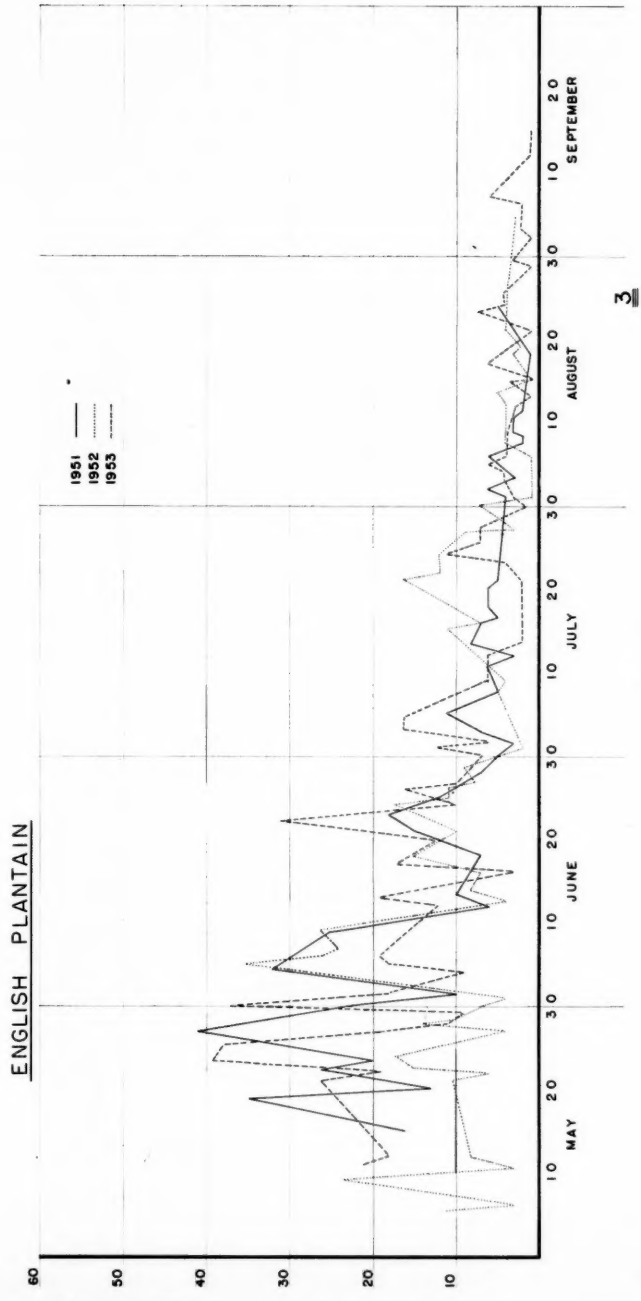

ENGLISH PLANTAIN
1951
1952
1953
60
50
40
30
20
10
MAY
JUNE
JULY
AUGUST
SEPTEMBER
10
20
30

Fig. 3

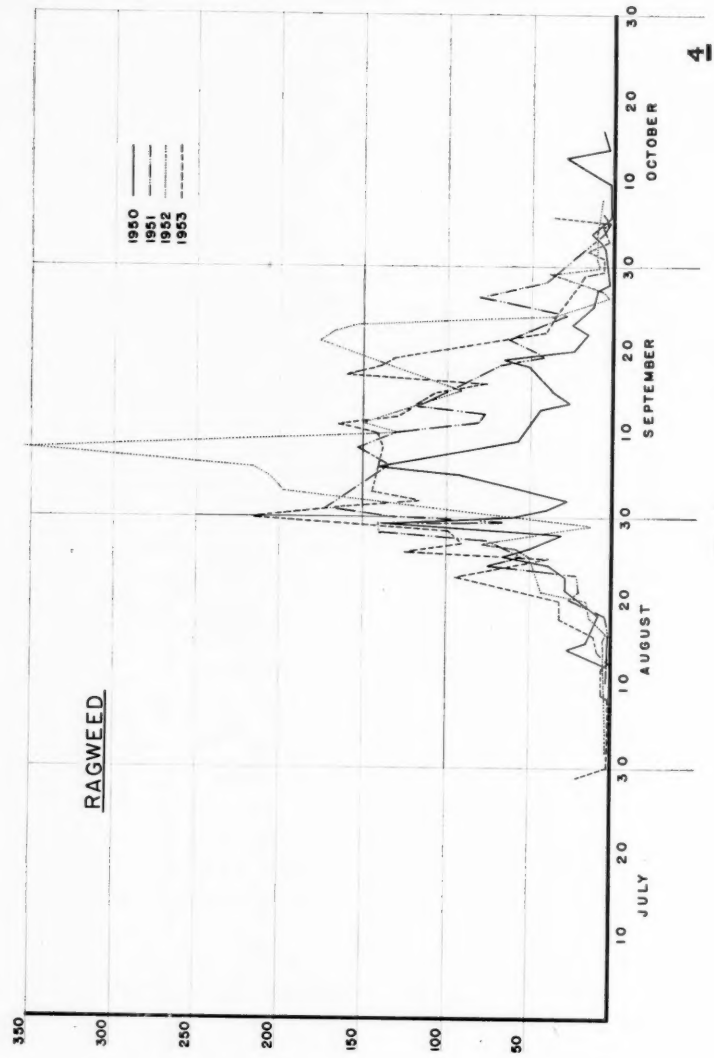

RAGWEED
1950
1951
1952
1953
350
300
250
200
150
100
50
10
20
30
JULY
AUGUST
SEPTEMBER
OCTOBER
41

Fig. 4

Grasses.—The grass season begins during the first or second week in May, grass pollen having been caught as early as May 3. Highest counts occurred during May and June, with a fairly abrupt drop in July, followed by a gradual reduction in numerical count extending through all or a good part of September. A perspective of the grass season's beginning, height, and gradual trailing off can be gained from Figure 2.

English Plantain.—The duration of the English plantain pollinating season parallels that of the grasses. It begins the first or second week in May and usually continues well into September, gradually trailing off after June. As a rule, English plantain pollen counts are numerically higher than those of the grasses. Figure 3 gives a perspective of the extent of the English plantain pollinating season with its height during May and June and gradual modification through September. Tables I, II, and III give the numerical pollen counts by months with total pollen grains caught for the year.

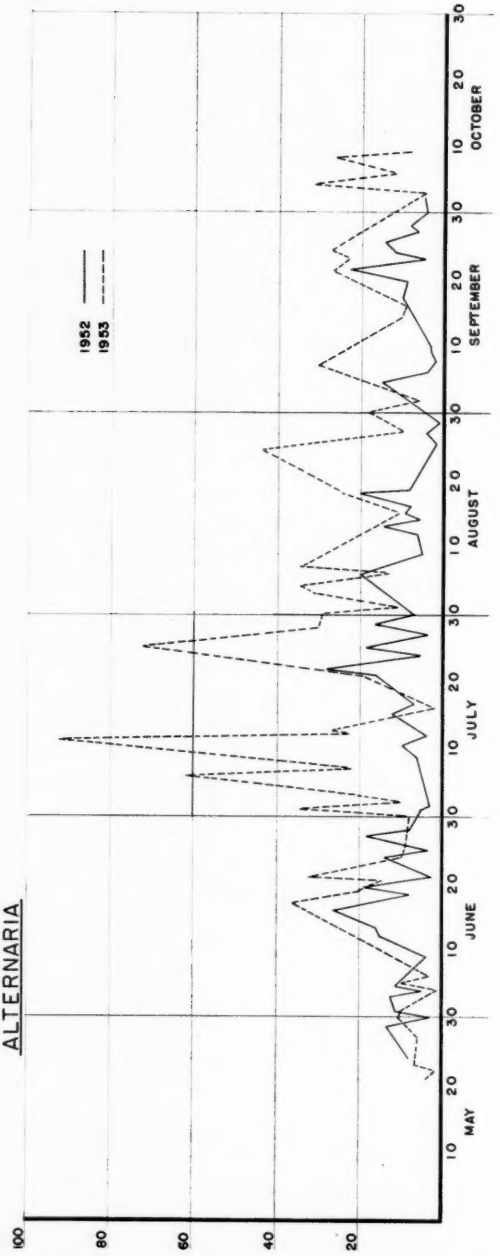
Ragweed.—Ragweed pollen appears during the first or second week of August, although it has been caught as early as July 30. The pollinating season extends to the first killing frost, which generally occurs no later than October 9 or 10. However, in 1950, when there was an extremely late killing frost, not until the latter part of October, ragweed pollen disappeared from the slides on October 16. The height of this season extends through the latter part of August into the first two or three weeks of September, with a preponderance of ragweed pollen grains being captured during September. Figure 4 demonstrates the variations in ragweed counts and the extent of the seasons through 1950 to 1953 inclusive. Tables I, II, and III show ragweed pollen counts by months.

Chenopod-Amaranth.—The chenopod-amaranth group, while seen on the slides occasionally during May, June, and July, do not reach significant numbers until August and September. These counts are illustrated in Tables I, II, and III.

FUNGI

Only *Alternaria, Helminthosporium,* and *Hormodendrum* were taken into consideration. Mold spores captured on the daily pollen slides were counted and tabulated throughout the pollen seasons of 1952 and 1953. These counts began with the tree pollinating season and were discontinued at the end of the ragweed season of each year.

From our counts it is evident that *Alternaria* is the most prevalent at-


ALTERNARIA
1952
1953
100
80
60
40
20
10
20
30
MAY
JUNE
JULY
AUGUST
SEPTEMBER
OCTOBER

5

Fig. 5

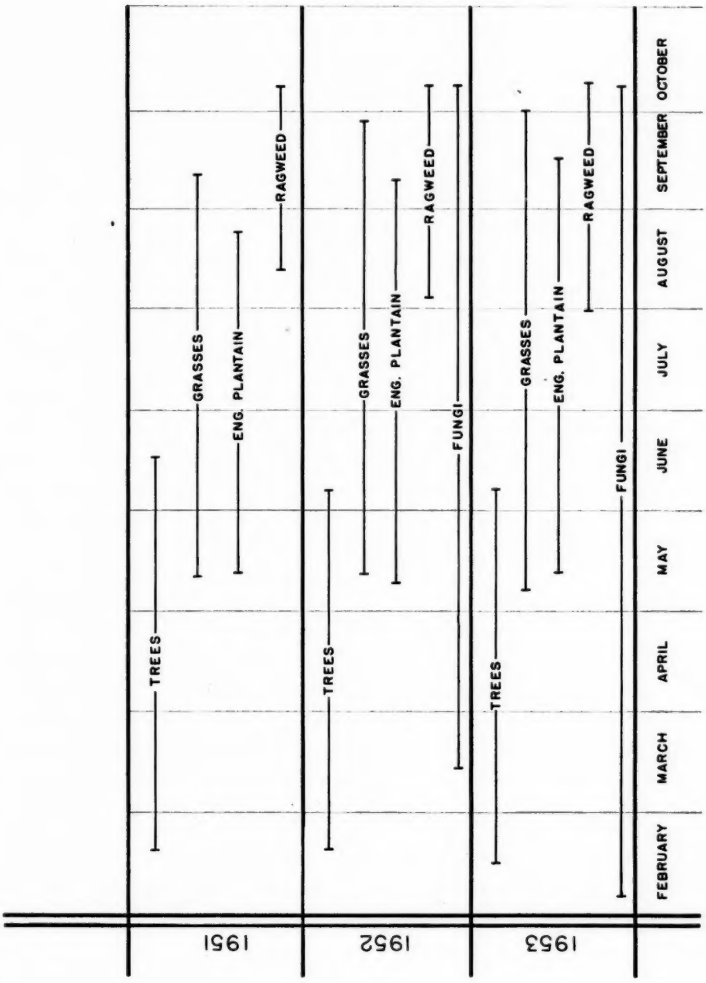

1951
1952
1953
FEBRUARY
MARCH
APRIL
MAY
JUNE
JULY
AUGUST
SEPTEMBER
OCTOBER
TREES
GRASSES
ENG. PLANTAIN
RAGWEED
FUNGI

Fig. 6

TABLE IV. TOTAL MOLD SPORE COUNT BY MONTHS, 1952

Fungi	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Total
Alternaria	1	3	0	41	256	145	142	137	5		730
Helminthosporium	2	4	0	2	36	32	11	19			106
Hormodendrum	3		3	125	117	4	6	197			455

TABLE V. TOTAL MOLD SPORE COUNT BY MONTHS, 1953

Fungi	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Total
Alternaria	1	0	5	48	237	548	450	277	86		1652
Helminthosporium	1	1	0	29	31	87	52	36	11		248
Hormodendrum	8	1	8	109	625	91	242	54	2		1140

mospheric mold spore in this area. *Hormodendrum* is a fairly close second with *Helminthosporium* third. See Tables IV and V.

Atmospheric mold spores in general are most prevalent in June, July, and August. However, both *Alternaria* and *Hormodendrum* occur in appreciable quantities throughout the latter half of September.

Figure 5 illustrates the duration of the periods over which *Alternaria* spores were captured.

It can be seen that the tree pollinating period overlaps that of grasses and English plantain, while the grass and plantain pollens, particularly the former, are caught well into the ragweed season.

Mold spores are caught during all the pollinating seasons in some quantity.

COMMENT

Although the pollen and mold spore counts in the Asheville area have not proven impressively high, it is the author's experience that the incidence of pollen and mold allergy is on a par with other areas in which he has practiced: notably, Richmond, Virginia; Shreveport, Louisiana; and Greensboro, North Carolina. In general, we have learned to expect symptoms to vary concurrently with the pollen and mold spore counts.

SUMMARY

Atmospheric pollen and mold spore counts were done in Asheville, North Carolina, during the pollinating seasons of 1951, 1952, and 1953. Appreciable quantities of tree, grass, English plantain, and ragweed pollen, as well as various mold spores and miscellaneous pollens, were caught during these periods.

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52 Page Avenue

THE USE OF CHOLINE THEOPHYLLINATE IN ASTHMATIC PATIENTS

Exploratory Data

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THIS PAPER is concerned with our experiences in exploring the use of oral choline theophyllinate in forty-seven asthmatic patients studied over a period of ten months. Discussed in some detail are the patients, the drug, the test procedure, and the results from which is made a final generalization. Protocols of typical patients are presented.

THE PATIENTS

We recognize the fact that, in our practice, the patients do not represent a fair sample of the general population of asthmatic individuals. Almost all have been referred by physicians who, themselves, treat mild or moderate asthma, and send us only those in whom their treatment has not been successful. A good number of these have had previous studies and, of course, either drug or injection therapy, or both. The relative ineffectiveness of such previous treatment is not considered a criterion of the physician's competence, but usually, and rather often, a crystallization of the best anti-asthmatic measures available at the time the patient was studied, although perhaps not always adequate by present knowledge.

Under ideal experimental conditions, the selection of subjects would have been completely at random, that is, with no "hand picking" of patients. We partially randomized those studied by choosing, on some days, every successive "new" asthmatic patient. On others, we took, as they came, every successive "old" asthmatic individual who was not completely responding to our usual medications. The drug was, therefore, being tested in what are commonly termed "difficult cases."

Obviously, there could be no control with well patients. Nor did we feel that it was necessary to measure the effects of the drug in those in whom we induced asthma by aerosol, allergenic or bronchospastic drugs, since none of these can be shown to be directly related to the patient's everyday environmental, infectious, exertional or emotional wheezing. Such asthma, induced in humans, is not always equivalent to ordinary attacks, and drugs which affect such types of bronchospasm behave quite differently in field trials. Controls would, for another reason, not have been suitable, because we knew from previous experience and the work of

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Dr. Clancy is an Associate Fellow of The American College of Allergists.

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Choline Theophyllinate (Choledyl®) supplied by the courtesy of Nepera Chemical Company, Inc., Yonkers, New York.

others that the drug took some days to manifest therapeutic results. Our other patients, not taking the medication, served as adequate control subjects in the widest and most general sense of the phrase.

We were, therefore, in a certain sense, selecting those asthmatic patients whose patterns of bronchospasm showed them to have been continuously wheezing, however mildly, for some days, weeks, or perhaps months. During this period they were, as usual, partially or temporarily relieved by other oral medications. This preliminary clinical trial, therefore, measures the effectiveness of the drug, and, when it is effective, compares it to previous medicines. In this type of therapeutic experiment, there is no need to issue the drug *and* a placebo on a double blind basis. Exploratory studies of this type are, of course, not suitable for statistical validation.

Because the period of intense study was relatively short, and not during the pollen season when, as well, the mold content of the air was at its minimum, neither of these changing seasonal patterns had to be considered. And because these were patients in whom the dust diminution precautions either had not been initiated at all, or had been in effect and stabilized for some time, we did not have to concern ourselves with any marked changes in environmental conditions.

Since all of the patients had had other medications, with some moderate, little, or poor response, and, as well, were suffering from almost continuous mild, moderate or severe bronchospasm, we felt that we could rule out the so-called "placebo-reactors." Had these patients been suggestible, other oral medications would have proven this point in the patients previously treated by us. We acknowledge the fact that the "new" patients, having been referred to us, might have been in a highly suggestible state. Since there was no obvious difference in type or duration of therapeutic response, this objection cannot be sustained, although the group was too small for us to be certain as to the extent of this variable. The continued excellent effect of the drug in those patients in whom it was efficacious would appear, in some degree, to rule out the effects of suggestibility.

Nor do we feel that the immunologic response to the skin tests in the "new" patients, or the continued injection treatment of the "old" patients, affected our results.

All we wanted to learn was whether choline theophyllinate, given prophylactically, would either lessen the number of attacks of asthma or increase the three-second and total vital capacity of asthmatic patients. The lack of randomization, placebo and double blind administration, induced asthma or controls, neither vitiate this experiment nor invalidate the generalizations we have cautiously and, we hope, objectively drawn from our data.

Of the forty-seven patients, only thirty-five could be used for study. Twelve either used the medication for too short a period of time, or else have not as yet reported their results. Some of these will undoubtedly be accounted for in a subsequent communication.

The patients' ages varied from four to seventy-two years, the duration of symptoms from one to sixty-five years. The group included twelve typically allergic patients with symptoms due only to inhalant exposure; seven emphysematous patients with no known clinical or experimental sensitivities; and sixteen subjects in whom combined syndromes appeared to be present, in that pollens, house dust and other inhalants caused attacks, as did infections and a number of other states, including emotion, exertion, changes in barometric pressure, and intercurrent infections.

Previous effective or ineffective drug treatment included almost every proprietary or prescription mixture known to us, among others, Hyadrine® and Hydrillin®, to which twenty patients had shown a good response and five no response. To Luasmin capsules, Quadrinal tablets, and T-Bardrin capsules there were thirteen who responded well, and six not at all. Seven patients had been relieved of their bronchospasm by a mercodeinone-potassium iodide-ephedrine mixture which did not help five others. Six had all reacted favorably to ACTH, with no failure. Of nine on cortisone, four had done well and five had not been favorably affected. On the other hand, of ten on Meticorten® therapy nine had done well. All six of six others could be kept symptom free on a "round the clock" administration of a standard potassium iodide-ephedrine-phenobarbital mixture. The responses, favorable or unfavorable, appear to follow no particular pattern, some patients requiring as few as two of the medicines listed, while others worked their way through three, four or five. The numbers overlap, and no conclusions are drawn from this phase of the study.

THE DRUG

Theophylline is known to be the most active of the xanthine derivatives. With ethylene diamine it has been used, since 1937,[4] intravenously with signal success in status asthmaticus. Gastric irritation, due to the release of free theophylline, and slow absorption, with variable blood levels below therapeutically effective amounts, have limited its oral use. The combination of theophylline with choline has been reported as a means of lessening such irritation and increasing such absorption, so that both larger doses might be given and higher blood levels achieved. Studies by Duesal et al[2] have shown a solubility five times greater than oral aminophylline. Gagliani et al[3] have demonstrated a 75 per cent higher blood level than that seen with equivalent doses of oral aminophylline. In a study by Katz and McCormick,[5] it was stated that over an eighteen months' period, doses of 100-200 mg, given three to four times daily, led to a decrease in the adjuvant use of oral bronchodilating agents in a group of fifty patients, of whom only one developed gastrointestinal symptoms. Dann et al[1] administered the drug similarly to eighteen asthmatic subjects for a period of one week to three months, in doses of 800 mg to 4 gm daily. In four of five on whom vital capacity studies were done, objective evidence cor-

roborated the subjective improvement noted. In six of the eighteen there was no, and in two others only slight, improvement. In nine (or in half of the number studied), the results varied from excellent to dramatic.

We were particularly interested in the fact that the investigators varied so widely in their evaluations, those quoted reporting such good effects, while others (unpublished data) felt that the medication was therapeutically ineffective. To this question, we feel we have a partial answer.

TEST PROCEDURE

Each patient had, at the time of administration or in the immediate past, received a complete physical examination, with recorded height, weight, blood pressure, three-second and total vital capacity studies, chest and usually sinus x-rays (electrocardiogram when indicated), with complete blood count, blood smear, urinalysis, sedimentation rate and serologic tests. Each was skin tested by the pressure puncture, and usually by the intradermal test, or both. The previous medications, when known by the patient, or from previous reports to the physician, were listed, and their effects noted. This information was at hand for our "old" patients. Each "new" patient was then given choline theophyllinate in doses of 200 mg three or four times daily, that is, after each meal and at bedtime. No patient was told that the drug was new, or that a therapeutic test was being done. None were warned of side effects. None were promised relief. In other words, the drug was issued as just one more medication in patients who had previously similarly been given many other prescriptions.

RESULTS

Of the thirty-five patients studied, twenty-two reported good relief, sufficient to warrant the satisfactory continued use of the medication in preference to other drugs. In seven others, there was no noticeable improvement, and in five in all, poor results associated with gastric distress, warranting discontinuation of the prescription. One patient was, on three occasions when she took four tablets daily, 200 mg each, kept awake all night.

It was at this point in the study that we found ourselves in a quandary. Our results appeared to straddle those of the other investigators. Once again we summarized the patients' histories, choosing one allergic patient who *had* been helped for comparison, if possible, with one who had failed to respond. The same was done with the nonallergic patients, evaluating one who was relieved with one who derived no benefit. The exact procedure was once more followed with the patients with combined syndromes. Using this classification, we could find *no* patient in the so-called nonallergic infective group who had failed to respond favorably. All seven did not only do well, but enthusiastically and extremely so.

This helped solve, in part, the question posed by the literature. The in-

vestigators who had reported excellent to dramatic effects were, none of them, allergists, and the patients they treated were not allergic, but rather suffered from emphysema, and chronic bronchitis—the so-called "asthmatic bronchitis." The allergists who reported on the ineffectiveness of the drug were dealing chiefly with patients with acute asthma, undoubtedly allergic in nature.

Other ancillary conclusions forced themselves upon us. The xanthines are, among other things, respiratory stimulants, supposedly acting directly upon the respiratory center. They would, of course, help the emphysematous, bronchitic patient. We do not know why this takes several days to become apparent, unless such good effects tend to self perpetuation, as is often seen in diuresis induced by the mercurial agents. The antispasmodic effects of the xanthines in these patients appear to be negligible, although undoubtedly present. The typical allergic patient requires more treatment directed against the bronchospasm and little stimulus of the respiratory center. Intravenously, the drug appears to act well in allergically induced bronchospasm, but when taken by mouth in the older, emphysematous, nonallergic (by present definition) group, it acts equally well.

Rearranging the data showed that all seven nonallergic patients were helped. Of the twelve allergic, eight were better and four not improved. Of the sixteen with combined syndromes, seven were improved and nine unimproved. These equivocal responses would suggest that although one part of the picture is clear, nevertheless, by present-day diagnostic procedures, some other factor has, perhaps, so far eluded us. Circulation time studies and pulmonary hemodynamics may help clarify these divergent responses.

One more interesting fact illuminates another aspect of the treatment. There appeared to be no diminution in therapeutic effects over a long period of time—in some of the published series, for two years. The xanthines are known to be different from most other drugs in this very quality. Coffee and tea can be taken daily for decades, with no lessening of the stimulation, and no need, after a lifetime of use, for larger daily doses.

REPRESENTATIVE PROTOCOLS

1. *Allergic Patient—Good Response*

M. B., a female nurse, aged twenty-two, with asthma of eighteen months' duration, beginning September, 1953, was hospitalized from January to March, 1954. On physical examination no abnormality was discovered, except moderate bronchospasm. Vital capacity was 2800 cc in three seconds (predicated normal, 3500 cc), blood eosinophilia was 9 per cent, and all laboratory studies were normal. Skin tests were positive for grass, ragweed pollens, and house dust.

Drug Treatment—There was little or no response to ephedrine, iodine, sedatives, and antihistaminic agents. Intravenous ACTH was only partially effective, and oral cortisone was without effect. The patient was relieved only by epinephrine 1:1000, 0.12 to 0.4 cc subcutaneously every four to eight hours. In February, 1955, choline

theophyllinate was given, 200 mg four times a day, with an ephedrine-iodide capsule to be taken at bedtime. The vital capacity increased to 3000 cc. The attacks have lessened from three to four daily to only one or two occasions of mild wheezing once a week. The environment has not been changed. Injection treatment for the pollen and house dust sensitivities has, however, been initiated. The choline theophyllinate has been taken daily for four months with consistently good effect, but with return of wheezing when it is omitted.

2. *Allergic Patient—No Effect*

V. B., a twenty-four-year-old male mechanic, had a history of atopic eczema in infancy and asthma since early childhood. His symptoms were perennial, with exacerbations from September through frost and later. Physical examination showed typical bronchospasm. Vital capacity was 2700 cc in a three-second test (predicated normal, 4300 cc), and blood eosinophilia was 8 per cent. Skin tests were positive for ragweed pollen, molds, and house dust, and there were positive reactions to many foods. There was no response to all trial diets.

Drug Treatment—Both oral cortisone and intravenous ACTH were ineffective. A prescription containing ephedrine, iodide, phenobarbital, mercodeinone, and tr. stramonium gave moderate relief if taken in 5 cc to 10 cc doses every two to four hours, day and night. Choline theophyllinate in doses of 200 mg four times daily in no way changed this patient's clinical course.

If the opportunity to study this patient again had presented itself, we would have increased the choline theophyllinate day by day up to one gram four times daily. Regretfully, we have to record that he was not helped by us. He has since moved to Arizona.

3. *Nonallergic Patient—Good Response*

E. S., a female secretary, aged sixty-nine, had a history of asthmatic bronchitis of twenty-one years' duration. Her symptoms were perennial, with exacerbations each winter, and upon exposure to cold, dampness, and respiratory infections. The physical examination revealed emphysema and bronchitis. Her three-second vital capacity has ranged between 1800 cc and 2500 cc (predicated normal, 4100 cc). She showed no response to khellin and cortisone, and poor, although some, response to ephedrine-iodide-aminophylline mixture. With choline theophyllinate, 200 mg after meals and at bedtime, there has been a steady improvement, no attacks, and a continuing sense of well-being for three months.

Because this group of nonallergic individuals contained no patient who did not react favorably, our protocol pattern is not symmetrical. We take the opportunity, therefore, of including a second protocol from this group of patients.

4. *Nonallergic Patient—Good Response*

R. R., a sixty-three-year-old man employed as a truckman, gave a history of chronic bronchitis for twenty years, with wheezing and shortness of breath upon exposure to cold air and respiratory infections, most marked for the last thirteen years. Coughing produces, with difficulty, a frothy white sputum. No cardiac symptoms have been present.

The patient presents a moderate emphysema, with scattered wheezing throughout the lung fields. The remainder of the physical examination is that of normal health. Vital capacity was 2600 cc in three seconds (predicated normal, 4500 cc). All laboratory studies are those of normality. Repeated x-ray films of the chest have been interpreted as showing pulmonary emphysema and evidence of chronic bronchitis.

The patient achieves good symptomatic relief, lasting two to three hours, from ephedrine-phenobarbital-aminophylline mixtures taken orally. These must be aug-

mented by bronchodilating nebulizations regularly for sudden episodes of wheezing. After three days of choline theophyllinate, 200 mg doses with meals and at bedtime, there was a marked decrease in dyspnea and increased ability to expectorate. There has been, to date, no necessity for the use of bronchodilating agents, for a period of approximately eight weeks.

5. *Combined Allergic and Nonallergic Wheezing—Good Response*

A. R., a housewife, aged thirty-nine, has had bronchial asthma for twenty-five years, with exacerbations during the peak of the pollen season, also respiratory tract infections during the winter months. For the first ten years of wheezing she experienced exacerbations and remissions, but has had few remissions since.

Except for moderate obesity and evidence of bronchospasm, all studies were those of normal health. All proprietary and prescription mixtures give some temporary relief. Following ACTH therapy there is clearing, with recurrence in three or four days. Choline theophyllinate, 200 mg after meals and at night, gives complete relief for daytime wheezing, but the patient continues to awaken at 4:00 a.m. in bronchospasm, requiring additional medication. It will be interesting to observe this patient during the pollen season.

6. *Combined Allergic and Nonallergic Wheezing—Poor Response*

E. R., a fifty-six-year-old male executive, has bronchial asthma of so many years' duration that the initial attack cannot be recalled. He has perennial symptoms, with summer and fall seasonal exacerbations due to pollens, and winter symptoms due to infection, exposure, and exertion. When the patient first came to see us he was taking Luasmin capsules (Brewer) every two to three hours. Physical examination showed moderate to severe emphysema, with bronchospasm. The skin tests were positive for pollens, house dust, and animal danders. The vital capacity was 2500 cc in three seconds (predicated normal, 3400 cc). Choline theophyllinate, 200 mg after meals and at night, caused "epigastric burning" and refusal to continue the medication. The patient has since been completely controlled with Meticorten, 5 mg twice daily.

GENERALIZATION

Aminophylline has been used for years with contradictory results, although the best effects occur when it is given intravenously, in almost all types of bronchospastic patients. By mouth, it has been used adjuvantly with ephedrine, phenobarbital, antihistaminic agents and other drugs. Under these circumstances, the theophylline effects are difficult to assess. An exploratory study directed towards measuring the cause of such unpredictable results with a salt (choline theophyllinate) known to be absorbed, and in amounts up to therapeutic levels, demonstrated no patients in the older emphysematous bronchitic group who did not benefit. Although asthmatic patient responses to medicines cannot be categorized so neatly, it appears that the drug is also useful in some typically allergic patients. Its chief virtue, it is suggested, would be in those requiring respiratory center stimulation. In these, the medicine should be administered in doses of 100-200 mg or more, four times daily (at mealtimes and on retiring) for a period of at least one week. In the present, and in previous studies, neither habituation nor decreasing effects have been noted nor expected.

Further studies are in progress, which will deal with choline theophyllinate as prescribed for this special group of patients.

SUMMARY

Choline theophyllinate was issued to forty-seven asthmatic patients varying in age from four to seventy-two years, suffering from representative types of asthma from one to sixty-five years. The dose was 100-200 mg three or four times daily. Of the thirty-five patients who were suitable for study, five demonstrated gastric distress, and one wakefulness. Twenty-two (including the wakeful patient) reported good relief and a desire to continue with the medication. Of these, all of the older nonallergic emphysematous group, without exception, showed marked improvement, as demonstrated by absence of wheezing or the presence of mild transient spasm requiring no additional medication. The vital capacity increased, as shown by the total and the three-second expiratory tests.

In seven patients, there was no noticeable change in the severity or the duration of the asthma. But in *all* groups except the emphysematous bronchitic, there are, as yet, inexplicable cases of good and no relief. Further studies may demonstrate whether this would have been true of a larger series, which we plan to subject to statistical analysis. The responses to the drug may, perhaps serve as a diagnostic, as well as a therapeutic, measure.

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75 Bay State Road
Boston 15, Massachusetts

NEW SUSTAINING MEMBERS

Raytheon Manufacturing Company, Waltham, Massachusetts, producers of Micronaire electrostatic air cleaners, and the Vaponefrin Company, Upper Darby, Pennsylvania, manufacturers of Vaponefrin solution and nebulizers, have joined the ranks of Sustaining Members of the College. Their additional support of the College through this type of membership is much appreciated.

DOMESTIC AND INDUSTRIAL COMPONENTS OF INHALANT ALLERGY

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IT IS the purpose of this paper to point out some remarkable features of similarity and dissimilarity between industrial and domestic factors of inhalant allergy. The allergist has the responsibility of making an etiologic diagnosis, the accuracy of which may have a decided influence upon the patient's source of income as well as upon his comfort and good health. To advise a patient to correct or remove some domestic environmental feature does not place too great a burden of responsibility upon the physician. A "trial and error" regimen has often been of great assistance in extending relief to the patient. This great burden of responsibility however, is of primary consideration when advice is sought concerning an industrial component of inhalant allergy. Without positive assurance of a satisfactory result, the allergist should be somewhat reluctant to remove an individual from a position of employment for which he, the patient, may have been well trained and highly experienced.

Though the basic components of inhalant allergy may be identical regardless of geographical location, the ultimate agents of cause will be dependent upon the type of industry found in any particular area. The industries of Georgia and Florida are comparable to those of Iowa and the mid-west in only the most remote manner. In the same vein, many trades and types of manufacture will be common to all areas of the country. With this in mind, let me take a few minutes to describe two or three representative instances in which domestic and industrial components of inhalant allergy have appeared to be in union or in open opposition to the production of discomforting or disabling symptoms. I shall not give the detailed features of each histroy but will assume that each of these individuals has nasal or bronchial complaints of sufficient degree to warrant allergy investigation and management.

The three gentlemen comprising my first comparison are engaged in the bakery business. Their histories and the presence of their symptoms are relatively common to members of their trade, regardless of the part of the country in which they may reside.

One of these three now holds an executive position after several years of training and experience in the production section of the business. In his earlier days, he did admit to some slight nasal irritation upon exposure to flour, but at no time were his complaints a source of marked distress nor disability. Within the past four or five years, a progressive degree

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of asthma has been noted with symptoms occurring in perennial, sporadic fashion. Prolonged attacks, with little relief, will follow close exposure to flour on those occasions when he is unable to avoid this substance as an inhalant. He is able to enjoy corn, rye and wheat in his daily diet without the appearance of allergic symptoms. Skin tests have shown marked, immediate positive reactions to these three grains. His problem did not require any major changes in his business. He continues to be a capable bakery executive free of symptoms, but with a remote control type of supervision over production in his business.

Baker No. 2, however, is in a situation somewhat different from No. 1. He is in the production end of baking, having started his training and experience two years prior to the onset of his asthmatic attacks. Originally, symptoms were present only in, and exacerbated by, his working environment. Since 1953, he has failed to notice any aggravation of his respiratory complaints by his type of employment. He does admit daily, persistent distress. He has offered the opinion that the ingestion of grain foods causes some recent increase in severity of his discomfort. Skin tests were definitely positive for all major grains. A cereal-free dietary routine has permitted this patient to exist with less trouble both on and off the job. His asthma has persisted in spite of varoius attempts at environmental precautions and protection. At present, he is free of inhalant allergy—disability insurance, a grain free diet for the past month, and a trial separation from his employment have afforded complete relief. The immediate recurrence of asthma is predicted upon his return to the bakery. It is this type of allergic individual who must seek other forms of livelihood, even though he has had years of experience in this field.

Baker No. 3 differs from the two preceding recitations. His nasal and bronchial complaints have been present for thirteen years in perennial manner with aggravation during the ragweed season. Concern was expressed regarding the possibility of his business being a primary etiologic source, since his inhalant allergy was present throughout the year. He was suspicious, but not convinced, of this probability. Investigative procedures, absence of clinical or skin test grain sensitivity, adequate ragweed, mold and dust therapy, and a thorough trial have shown the fallacy of our original concern. Baker No. 3 is not now sensitive to his industrial environment. To paraphrase an old wheeze, not all asthma in bakers is bakers' asthma.

These three brief reports are significant. They are similar and yet they are dissimilar. In one, the industrial component is of no consequence; and in the others, industry plays a major and a minor role, the importance of which is plainly evident.

It is controversial whether or not inhalant allergy will adequately explain the activation or aggravation of allergic dermatoses. The influence of this important subject must be based upon the individual response to

corrective measures of avoidance and specific therapy. In resistant or particularly stubborn problems of this nature, inhalant sensitivity can be shown as a predominant factor. Thorough search would perhaps reveal an industrial influence. These two brief instances will serve to bring to your attention the part that environmental substances may have in this regard.

A persistent, scaling, itching skin eruption of generalized distribution had been a source of distress to a young housewife. Her history revealed that childhood eczema had spontaneously cleared, with freedom from any skin lesions being enjoyed for approximately ten years. About one year prior to her original visit, she noted the onset of progressive skin lesions that had eventually produced a variety of diagnoses and as many forms of therapy. Her home at the time of onset was in Minneapolis which, I believe, will be of some importance in this report. Clinical confirmation of investigative procedures has shown this patient to be sensitive to dust and molds. Specific therapy with these extracts has produced skin clearing. Her residence in Minneapolis and Cedar Rapids, both of which are cereal mill cities, adds weight to the importance of inhalant mold sensitivity. Removal of this patient from these areas of heavy atmospheric mold resulted in spontaneous improvement. Respiratory symptoms have been observed during the height of the summer mold seasons. These, however, are of minor significance and have responded well to treatment. This recitation illustrates the influence that local industry may have upon persons in the community even though the affected individual may not have a close association with the source of the causative substance.

Inhalant sensitivity as a cause of allergic dermatitis should not be given first consideration. Failure of elimination and avoidance of more commonly suspected agents to produce a satisfactory end result should suggest the probability of inhalant etiology. Adequate specific ragweed therapy controlled the hay fever symptoms of a middle-aged housewife. Other measures, however, had no control over a persistent, perennial, generalized dermatitis. When her known sensitivity for dust was abated by environmental correction and specific dust therapy, a clear skin was maintained. These two instances are considered as definite indications that some allergic dermatidides may be due to inhalant sensitivity, of both domestic or industrial origin.

The importance of industrial allergy is marked in that community whose livelihood is closely associated with potential sources of trouble. The more potent the allergens, the more disability will arise from these agents. To practice allergy in the agricultural area of the Middle-West is to see many patients whose respiratory symptoms are based upon their grain or mold sensitivity. There is the farmer who is unable to work in his harvest field; there is the cattle feeder who cannot work in close contact with his stock or their feed; and there is the mill worker who is

unable to continue in his occupation. Because Iowa is a leading farm state, much of our industry is related to this task of feeding the nation and the world. In this locality, it is not uncommon to see examples of recognized industrial allergies in other types of employment, but the greatest majority of inhalant allergy allied to industry will be related to growing or processing grain.

A striking example of inhalant allergy in a cereal mill worker was brought to attention in recent weeks. Initial symptoms of asthma had been noticed after two and one-half years' employment. Progression in severity and duration of symptoms had been recognized. This person had requested a change in type of occupation because of immediate symptoms upon exposure to oat dust. On those occasions when his work called for him to "blow-out" an oat bin, he was forced to leave his duties, seek medical aid for relief and retire to his home where he was confined for two or three days. Eventual clearing of respiratory distress permitted him to return to work with a repetition of the acute difficulty. On those occasions when his task was that of transferring grain by closed suction from elevator to bin, he was able to remain on the job. Immediate and violent asthma appeared when the bin was being cleaned. The foreman was of the opinion that this man was "gold-bricking" because the bin-blowing-out was an unpleasant task. Investigation revealed markedly positive reactions for *Alternaria* and grain dust. In this instance, specific therapy was not advised because the causative agents could be adequately avoided—at least for the time being—with a change in type of occupation within the mill. The patient remains clear of asthma and has not missed a day of work in the past six weeks. With mold sensitivity now established, it will be interesting to learn whether or not this patient will have seasonal symptoms during the height of the *Alternaria* in the atmosphere this summer.

In this same large mill, there is an office worker with a similar problem but with a somewhat different solution. History here reveals the onset of bronchial asthma in childhood. Original symptoms were seasonal in character with eventual perennial attacks. This patient noted a remarkable aggravation of his respiratory discomfort shortly after beginning his employment at the mill. Following skin test confirmation of his mold sensitivity, specific therapy was instituted and has been productive of highly satisfactory results. Individualization of therapy in each of these cases has permitted them to remain on their jobs and to live a normal, comfortable life.

The effects of such an environment are not limited to those individuals employed in these immediate surroundings. One young man had been hospitalized at frequent intervals because of severe, intractable asthma. Residence in the country was conducive to complete freedom. A return to his original home in the shadow of a cereal mill brought a recurrence of his asthma and hospital admissions. Usual measures of oral, rectal

and parenteral therapy for the ambulatory asthmatic patient were unsuccessful in offering any token of relief. His problem was answered by a change of local residence to another section of the city.

The Middle-West has two mold seasons, but in this immediate area, the mold sensitive patient may have perennial complaints with seasonal aggravation. The spring season has its onset in middle or late March, somewhat earlier than tree pollen is noticed on the exposed slides. Less atmospheric mold is present during the latter part of May and through June. In mid-July, well before the classical ragweed season in August, mold patients will experience marked respiratory symptoms. These are prolonged into October and November. Incidentally, one suggestion of mold sensitivity in seasonal respiratory allergy is the absence of any definite seasonal limitations regarding onset and cessation. These are decidedly variable in individuals as well as in seasons. Surveys have shown the predominant mid-western molds to be *Alternaria, Helminthosporium, Hormodendrum* and the *Aspergillus* group. *Penicillium* molds are present but not to the degree of these spores previously mentioned. Investigative procedures should be all-inclusive for available molds and not limited to only a few, major extracts of this type.

My own local community has the largest cereal mill in the world at the northern border of the business district. On the southern edge of the city is a huge corn-processing plant. Grain elevators for storage and shipment occupy the western section of the city, while another large cereal mill is located on the northeast side of town. Surrounded in this way by grain storage and processing plants, the average allergic person is exposed to multiple allergens regardless of the direction of the wind. Interestingly, this is a purely local problem. The fortunate patient can obtain temporary relief by removing himself from the immediate vicinity. The sensitive patient can find complete comfort by a change of local residence, not necessitating a dramatic, climatic change.

Without a history of prior inhalant allergy, symptoms of respiratory distress may be noted in mill workers within twelve to twenty-four months after initial close exposure. A hurried review of several case histories reveals that this is the average "incubation period." Of course, some individuals will have marked symptoms from their first day of employment. In these instances, known pollen, mold or dust sensitivity had been recognized in past years. These workers should have been advised to seek some other form of occupation. The preventive aspects of industrial allergy hold more promise than actual correction or therapy of resultant symptoms.

Modern industry is acutely aware of the necessity of dust control. This is particularly true in the grain milling business. There are serious dust problems in all phases of the industrial picture, but my source of information has limited his remarks to this single type of industry. The

Quaker Oats Company has courteously supplied the details of their attempts to solve their dust problems.

The hazards of fire and explosion are of primary concern, in that every business has the responsibility of protecting human life and property. Employes must be guaranteed sanitary and pleasant working conditions. Dusty or irritating surroundings tend to increase the rate of employe turn-over. Conservative estimates have placed the cost of $250 to $300 on each employment termination. To indoctrinate and educate a person for a special type of work is even more costly should that trained individual cease his employment after he has gained months or years of valuable experience. Responsibility to the community demands that industry make every attempt to confine and collect the dust within their own operating area. Installation of expensive equipment is an aid in preventing atmospheric contaminants from being carried to homes and offices of the residential and business districts of the city.

Cereal grain dust has a high feed value for livestock and poultry. Reclamation of the tiny particles of grain, hull or chaff is an imporatnt part of the economy of wise milling operation. Employe absenteeism is another facet of operational expense. Cereal and grain dust irritation or sensitivity could be a big factor in enforced absence from work. These then, are the reasons for this large industrial plant to consider an adequate dust control system to be an essential part of operating procedure.

There are, of course, many different types of dust collectors and collecting systems. The sketch shown in Figure 1 will give an idea of the main principles used by this mill to corral grain dust. The actual operation is much more complicated than can be graphically presented. In fact, the oat-cleaning system of this Quaker Oats mill is comprised of thirteen floors of cleaning machinery. Batteries of machines may be in one giant collecting system or a single unit may be tied into a smaller system.

As the raw, uncleaned grain passes from a storage bin to a piece of grain-cleaning equipment, normal agitation causes the lighter dust to separate and rise. Drawn by an exhaust fan through a suction hood, the dust enters a primary collector or metal cyclone. Separated by rotary cyclonic action, the heavy dust falls to the bottom and is conveyed to the feed mill. The lighter dust, propelled by a fan, passes from the top of the cyclone into a secondary collector. This latter is actually a cloth filter of which there are many types. This stocking type utilizes a dust box at the top with subsequent discharge into cloth tubes or stockings. The special European flannel used in these filters has long fibers which retain the dust but permit the free passage of clean air. Automatic cleaners, moving up and down the stockings, prevent adherence of dust with resultant clogging of the cloth filter. The outlet at the bottom of the stockings transfers the dust to the same feed conveyor that carries material from the bottom of the cyclone. Since this system is entirely closed, the grain dust is confined and is thus controlled to a good degree.

The most efficient dust-collecting equipment will not prevent exposure to the employe in all instances of grain-milling operation. There are occasions when machinery must be cleaned by compressed air or dusty feed ingredients must be unloaded with hand-operated power shovels. It is

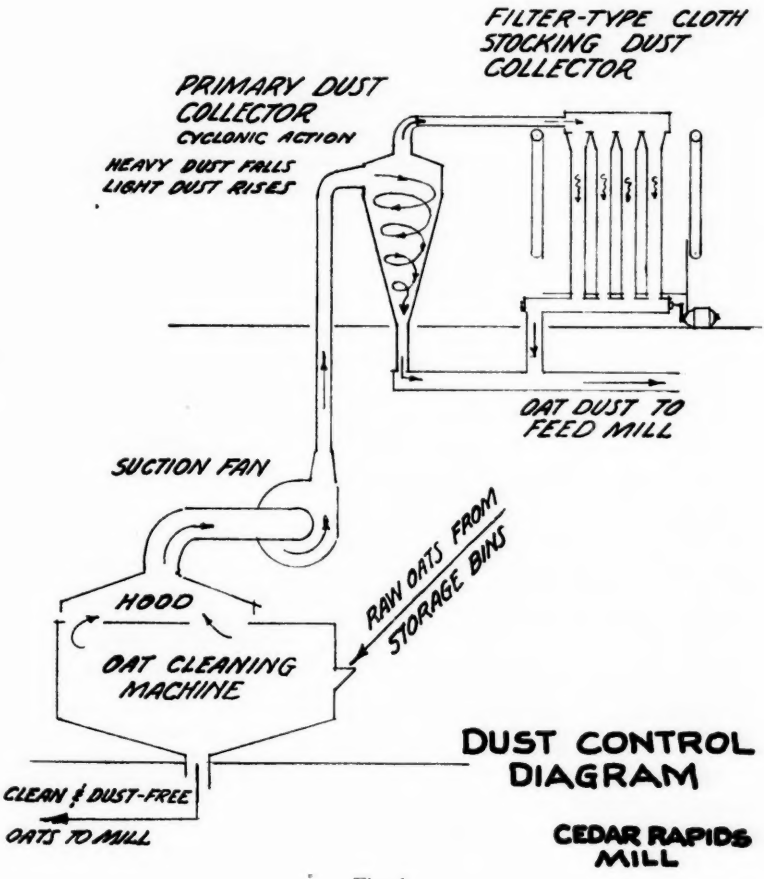

Fig. 1.

impossible to install an effective mechanical dust-collecting system in this open-area type of work. Here, it is necessary for the operator to wear a mask. By experience, this employer has found two types which answer his requirements. The Martindale protective mask is a simple affair, and is used where conditions warrant the operator's presence in non-toxic dusty areas for only a short time. The AO-R2000 respiratory mask

(American Optical Company) offers real protection, contains an excellent filter and is worn in areas of heavy dust concentration. It has been stated that no industry has completely solved the dust problem. Locally the large grain mills are constantly aware of their responsibilities to their employes and to the community. This necessary expenditure of a considerable sum of money for constant study and research will lead to continual improvements in this important phase of milling operation.

The foregoing examples of industrial and domestic inhalant allergy have been cited for three reasons. They point out the need for good care, proper management and close attention to causative or contributing etiologic factors. They also serve to illustrate the necessity of co-operation between industry and the allergist for the benefit of the individual patient and the community. The measures for environmental control employed by a leader of grain-milling operations demonstrate and emphasize the importance of these procedures in industry.

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SYMPOSIUM ON HEALTH HAZARDS OF CHEMICALS

An estimated 3,300 accidental poison deaths result each year from misuse of chemical products. There are on the market today about a quarter of a million brand name chemical products for use in the home, farm, and industry, all of which are useful if handled properly but may become killers, cripplers, or destroyers of property if not used correctly. As part of a campaign to spread information about these products and their hazards, The Committee on Toxicology of the American Medical Association will sponsor a symposium on health hazards of chemicals on December 29, 1955, during the annual meeting of the American Association for the Advancement of Science, in Atlanta, Georgia. The purpose of this symposium is to interpret new knowledge of chemical products to scientists in various fields, so that they in turn may use and spread the information. Participants in the symposium will be Lester M. Petrie, M.D., director, preventable diseases service, Georgia Department of Public Health, Atlanta; Wayland J. Hayes, M.D., chief of the toxicology section, Communicable Diseases Center, U. S. Public Health Service, Savannah; Irvin Kerlan, M.D., associate medical director, Federal Food and Drug Administration, Washington; and Mrs. Veronica Conley, assistant secretary, AMA Committee on Cosmetics, Chicago.

OCULAR ALLERGIES

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IF THE hereditary and degenerative diseases and local infections are excluded, we find that a large percentage of ocular diseases is associated with allergic manifestations. These allergic conditions may affect the eyelids, conjunctiva, cornea, sclera, uveal tract, lens, optic nerve and retina.

LIDS

Allergic dermatitis of the skin of the lids is quite common. The skin of the eyelids is particularly susceptible to inflammation because of its fine texture, thinness, and the exposed position it occupies. Usually, there is redness and swelling of the skin, accompanied by burning and marked itching in the early stages. Later, in the more chronic phase, the skin may present wrinkling and a brownish discoloration. Blepharitis and conjunctivitis are frequently associated with lid dermatitis.

Contact allergy is the most common form of acute eczema of the lids and is usually due to cosmetics or ophthalmic drugs. New causes of contact allergy are constantly being reported, and include jewelry, plastics, metals, clothing and various ingredients of such unrelated substances as insecticides and depilatories. The condition may be either unilateral or bilateral and occurs predominantly in women. Often, though the cosmetic is not applied directly to the eyelids, the lids may be the only site of the eczema. This results from the fact that the drug or chemical is not able to penetrate the thicker skin where originally applied, but is able in even the minimal amounts indirectly contacted to penetrate the lid skin sufficiently to produce the reaction.

Often if eczema of the eyelids is due to cosmetics, only the skin of the medial portion of the upper eyelid is involved at first. Usually the conjunctiva at this stage is not involved. In determining the allergen, careful history taking is, of course, of primary importance and it is well to remember that even though a cosmetic has been used without reaction for years the manufacturer may recently have changed the formula or the method of production. At present, most allergies due to cosmetics are the result of perfumes or impurities, since such notorious offenders as orris root and rice powder have generally been eliminated. The most important allergens today are the synthetic resins in nail polish, lanolin or cocoa butter and almond oil in facial creams, the indelible dyes in lipstick and certain chemicals in hair dyes and rinses. Allergies to eyelash dyes are infrequent and allergy to mascara, when it occurs, is due to the base used and not the dyes.

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When eczema of the eyelids is due to sensitivity to ophthalmic drugs, the reaction generally begins as a conjunctivitis since the conjunctiva is usually the focal point of contact. Characteristically there is severe itching and soon there develops papillary conjunctivitis and eczema of the skin of the eyelids. Conjunctival eosinophilia is present, whereas it is usually absent in eczema of the lids caused by cosmetics. The earliest evidence of eczema may be at the canthi if eye drops are the sensitizer, while the lid margins may be first involved if ointments are the cause. The most important drugs causing eczema of the eyelids are anesthetics, antibiotics, sulfonamides, mydriatic alkaloids, and mercurials. Frequently the vehicles, especially preservatives and ointment bases, rather than the active ingredients are the offending agents. Theodore[3] has recently stressed the fact that drug irritation rather than drug allergy may produce irritation of the conjunctiva. This reaction is differentiated from allergy in that often a follicular inflammation of the conjunctiva, without eczema or eosinophilia, results from the prolonged use of miotic alkaloids, such as eserine and pilocarpine and related synthetic products which are prone to deteriorate forming irritating end products. It is of great importance at times to make the distinction between these two types of drug intolerance, since drug irritation can be avoided by using properly prepared solutions of the same drug, while drug allergy requires substitution of a different drug.

Eczema of the eyelids may at times follow the systemic use of such drugs as bromides, phenolphthalein, antipyretics, iodides and barbiturates.

The emphasis that has been placed on contact allergy has tended to obscure the fact that other types of eczematoid dermatitis which are very similar in appearance do frequently occur and must be differentiated if therapy is to succeed. In addition to allergic dermatitis, infectious eczematoid staphylococcal dermatitis and certain generalized dermatoses, such as atopic dermatitis, neurodermatitis, seborrheic dermatitis and psoriasis, must be considered.

Infectious eczematoid staphylococcal dermatitis of the eyelids, secondary to blepharitis, meibomitis and conjunctivitis, is probably the most common form of chronic eyelid eczema. It is often difficult to distinguish this form of dermatitis from contact allergy by appearance alone, but in infectious eczema examination reveals: (1) blepharitis, with scaling and, often, small ulcers of the lid margins; (2) meibomitis, either diffuse or focal; (3) superficial epithelial keratitis; (4) strongly positive conjunctival and lid margin cultures; and (5) absence of eosinophils in the epithelial scrapings. Proper diagnosis is of the utmost importance, for the specific antibacterial treatment employed in infectious eczematoid staphylococcal dermatitis would of course greatly aggravate the hypersensitive skin of contact allergy, while the bland regime indicated in nonbacterial eczemas would provide only a more favorable environment for the bacterial process.

The eczema of the eyelids which occurs in certain generalized derma-

toses is distinguished by the fact that while the eyelids may appear to be the only area of skin involved, careful search will reveal skin lesions elsewhere.

CONJUNCTIVA

Allergic conjunctivitis produces various symptoms and findings, but most commonly itching, burning, foreign body sensation, photophobia and lacrimination are present in varying degrees. Mucoid discharge is a prominent finding, and frequently it is described as stringy or even rubber-like. There is a variable increase in eosinophils and in uncomplicated cases the culture is negative. However, superimposed bacterial infection is common.

Vernal catarrh is a special and interesting form of conjunctivitis which is often cited as the classic allergic disease of the eye and is so named because of its seasonal incidence. The attacks occur in the warm weather and become less acute as winter approaches. Typically, there are "cobble-stone" plaques on the lid conjunctiva, and in a smaller number of cases a limbal form of the disease appears. Many eosinophils are found in conjunctival smears. Treatment has usually been unsatisfactory, but recently many instances of satisfactory response to hormonal therapy have been reported.

Phlyctenular conjunctivitis is characterized by the formation of one or more pustules at the limbus of the cornea and is generally regarded as an allergy to tuberculoprotein, although rare cases as reported by Thygeson[4] appear to be due to other bacterial, viral or fungal proteins. The condition usually occurs in undernourished, debilitated children, and responds to improvement in diet and hygienic conditions and improves dramatically with the local use of cortisone and hydrocortisone.

CORNEA

Interstitial keratitis is usually found in patients with congenital syphilis and is regarded as an allergic reaction to the toxins of the spirochete present in other parts of the body.

Small punctate ulcers that may cover the whole cornea are frequently allergic in origin and may be due to contact allergens or foods. Most of these are due to local anesthetics and at times their continued use has led to irreversible damage to the cornea. Recurring dendritic ulcers have been reported as being due to food allergies by Lemoine.[1] In this connection, it might be well to point out that cortisone and hydrocortisone used locally in the eye have proved to be very beneficial in most allergic disorders, but that these drugs are definitely contraindicated in virus diseases, and that in dendritic keratitis their use has been reported to lead to perforating ulceration with all its dire consequences.

Keratoconus is believed by some[2] to be an allergic manifestation.

SCLERA

Since the sclera is protected by the conjunctiva, the only allergens that will affect it are those in the circulation. Diffuse and localized episcleritis and deeper involvement resulting in scleritis are principally expressions of allergy to tuberculoprotein.

UVEAL TRACT

There has been accumulated a considerable mass of evidence that uveitis is due in a large percentage of cases to allergy to toxins from foci of infection or tuberculoprotein. Recent findings would indicate that approximately one-fourth of the uveal inflammations of undetermined etiology may, however, be due to toxoplasmosis rather than allergy as was previously assumed.

Sympathetic ophthalmia is believed to be due to the sensitization of the uninjured eye by the uveal pigment of the injured eye, and it is interesting to note that cortisone greatly ameliorates the disease.

LENS

Atopic cataract is associated with allergy of the skin, and it is now generally believed that the intraocular inflammation known as phacoanaphylactic endophthalmitis that comes on following traumatic, surgical or spontaneous rupture of the lens capsule is due to allergy to lens substance.

OPTIC NERVE AND RETINA

Optic neuritis and retinitis may be due to an allergy to tuberculoprotein and from foci of infection, and a few cases of detachment of the retina have been reported as due to an allergy.

In all these ocular allergies, treatment consists in identifying the allergen and removing it from the patient's environment or desensitizing the patient to it. When this is not possible, such palliative measures as the use of epinephrine, antihistamines, or steroid hormones, should be employed.

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THE PROPHYLAXIS OF PENICILLIN REACTIONS WITH CHLORPROPHENPYRIDAMINE MALEATE INJECTION 100 MG PER CUBIC CENTIMETER

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MORE and more it is coming to be recognized that penicillin is not a "safe" drug. That is, it is realized that individuals who have received penicillin may become sensitized to it so that at the time of a subsequent dose, even after a lengthy period, the recipient may have a reaction. With the huge quantities of penicillin dispensed, large numbers of the population are likely to become sensitized so that a real danger exists of encountering severe reactions. Individuals who have not previously received penicillin may also show penicillin sensitivity. Peck, Siegal, Glick, and Kurtin[32] found that 5.4 per cent of 276 adults who had never received the antibiotic reacted "spontaneously" to skin tests with penicillin.

The types of sensitivity reactions to penicillin have been reviewed many times.[5,7,8,11,24,25] The incidence of these reactions varies from 2 to 16 per cent. They "cover almost the whole gamut of allergic reactions and immunological mechanisms."[24] Dermatitis, urticaria, and serum sickness are among the most frequent, but the most severe is anaphylaxis, and its greatest danger lies in death from anaphylactic shock. The problem of reactions to penicillin has become so serious that the antibiotic is said to be "the most common cause of drug allergy,"[24] and to head "the list of therapeutic agents in the production of undesirable reactions. It has replaced foreign sera as the most common cause of fatal anaphylactic shock."[15] Warnings appear frequently against the indiscriminate use of penicillin, pointing out the possibility of severe and even fatal reactions.[12,14,16,42] Welch[42] of the Department of Health, Education and Welfare of the Food and Drug Administration recently warned that "such (anaphylactoid) reactions to penicillin are rising in proportion to the ever-increasing use of the antibiotic . . . In the United States there are 200 anaphylactoid reactions due to penicillin every year, with a high proportion of these cases resulting in death—usually within five minutes after injection."

These warnings are certainly apropos in view of the serious sequellae to the administration of penicillin by various routes resulting in death or generalized exfoliative dermatitis, purpura, and Jarisch-Herxheimer

Study conducted under the auspices of the 3rd Marine Air Wing Medical Department, Marine Corps Air Station, Miami, Florida.

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reactions in syphilitic patients.[2,4,6,9,13,19-21,30,34] The first death attributed to anaphylactic shock was reported by Wilensky[44] in 1946. Waldbott[41] in 1949 reported an immediate anaphylactic death due to penicillin, and since that time there have been published reports of many others.[1,10,17,18,22,27,29,33,35,37,40,43] In addition, one can find reports of nonfatal or near-fatal anaphylaxis to penicillin too numerous to include here. Certainly not all such incidents have been reported. Welch, Lewis, Kerlan, and Putnam[43] in a brief survey discovered fifty-nine acute anaphylactoid reactions to penicillin which had not appeared in the literature.

Feinberg, Feinberg, and Moran[18] summarize their survey of penicillin anaphylaxis as follows: "Severe and even fatal reactions to penicillin are occurring with increasing frequency. The major symptoms are urticaria, asthma, shock, cyanosis, and unconsciousness. Probably any type of penicillin . . . administered by any route, can produce this type of reaction. This type of sensitivity . . . is usually induced by repeated courses of penicillin and occurs more frequently in those persons who are subject to other allergies . . . The immediate whealing skin reaction obtained with the scratch or intradermal test is diagnostic of the anaphylactic or atopic type of penicillin sensitivity."

As to the value of scratch or intradermal testing in indicating the probability of sensitivity to penicillin, there is not complete agreement.[24] Unfortunately, the longer the interval since a patient received a sensitizing dose of penicillin, the less likely the skin reaction is to be an immediate positive reaction, yet the patient may still be sensitive. The delayed reaction may persist longer. A negative result in patch testing does not guarantee against a reaction when penicillin is injected.

The administration of penicillin then is truly fraught with danger and there is no certain way of predicting when a severe or fatal reaction is likely to occur. This calls for extreme caution in the administration of the drug and inordinate reliance on the patient's history in an attempt to avoid reactions. Fortunately, a method has been found for the prophylaxis of allergic reactions to penicillin that greatly reduces their incidence and permits the administration of penicillin to individuals known to be sensitive to it.

This method is the administration of an antihistamine in conjunction with the penicillin. In his studies on hypoallergic penicillin, Simon[38] combined 3 mg chlorprophenpyridamine maleate (Chlor-Trimeton Maleate®) in aqueous solution with 600,000 units doses of penicillin, and encountered only three mild skin eruptions in the use of the mixture in 750 patients, a reaction rate of 0.4 per cent. Simon's further experience with 5,000 patients showed that the addition of an antihistamine to penicillin reduced the rate of reactions from 5 to 0.72 per cent.[39] Other investigators using Chlorprophenpyridamine maleate mixed with aqueous penicillin have noted an extremely low incidence of allergic reactions. With the use of this antihista-

mine it has been possible to administer penicillin to known sensitive patients without the occurrence of severe reactions.[3,23,26,28,31,36]

If the simultaneous administration of an antihistamine will effectively prevent allergic and especially anaphylactic reactions to penicillin, much of the hazard in its administration will have been overcome. This would be a boon to the general population and to the military services. Because of the frequency with which penicillin is prescribed in the medical divisions of the latter, the method of administering an injectable antihistamine with penicillin was studied to determine its efficacy and with the thought of recommending it as a routine procedure should the results warrant.

MATERIAL

The investigation to be reported was conducted in the dispensary at the Marine Corps Air Station, Miami, Florida, which controls all sick call and medical examining for the base. The study covered the period August 1 through November 30, 1954.

During that time every patient for whom an injection of penicillin was ordered was referred to the first author regardless of the department—enlisted sick call, officers' sick call, ear, nose and throat, or ophthalmic—to which he originally reported. Individuals presenting themselves in aviation examining were also included in the study. A decision was made in each instance whether the patient was to be one of a control series to receive penicillin alone or whether he would receive the antihistamine, chlorprophenpyridamine maleate in solution, combined with a dose of penicillin. The dose of each substance was determined, the injection given, and all records kept at one location.

When any patient was subsequently admitted to sick bay or seen in one of the clinics with a penicillin reaction, standing orders were to transmit the information to us for follow-up. No opportunity existed for overlooking any such reaction because the men either reported to our department or the corpsman notified us of all admissions to sick bay. The daily admission sheet served as a double check. In each instance of reaction, we reviewed the patient's history, the history as to previous administration of penicillin, and the indication for which penicillin was most recently given.

A total of 1,157 injections were given to 512 men during the four month period of study of the prophylaxis of penicillin reactions with chlorprophenpyridamine maleate in injectible solution. The patients ranged in age from seventeen to sixty years. The majority were twenty to thirty years old.

All of the men were ambulatory out-patients. Hospitalized patients were excluded from the series. Penicillin was administered for indications such as those encountered in general practice. Fifty-seven men, or 11.1 per cent of the entire group of 512, had had no penicillin prior to that administered during this study.

From the histories obtained from the patients, it was learned that fifteen

men had previously had a reaction to penicillin manifested as angioedema, hives, systemic or skin reactions, or serum sickness. That four others had had a reaction to penicillin could not be definitely established from the histories. They may have been nervous or have had a temporary vasomotor reaction rather than a true allergic reaction to penicillin. Therefore, these four were classified as indefinite reactors and excluded from computations of the per cent of reactors in the series.

The fifteen known reactors represented 2.9 per cent of the group of 512 men. However, they represented 3.3 per cent of the men previously receiving penicillin—that is, computing the percentage after excluding the fifty-seven men who previously had received none of the antibiotic. This further substantiates that increasing numbers of the population are becoming allergic to penicillin.

METHODS

In all, 540 injections of penicillin were given combined with chlorprophenpyridamine maleate. The dose of chlorprophenpyridamine maleate* was 20 mg, or 0.2 cc withdrawn from a vial containing 100 mg of the antihistamine in each cubic centimeter. After the antihistamine was drawn into the syringe, 600,000 units of aqueous penicillin were added. The syringe was rotated to insure adequate mixture, and the injection made in the usual manner. Recorded at the time of injection were the patient's name, his serial number, the date of the injection, the indication for penicillin, the doses of penicillin and of chlorprophenpyridamine maleate, any previous administration of penicillin, and any previous penicillin reactions.

As a control, 583 injections were made of 600,000 units penicillin each with no added antihistamine. The same kind of record was made for the patients receiving penicillin alone.

Each of the fifteen known reactors received an injection of penicillin whenever it was ordered. Three of these men had their previous penicillin reaction from nine to eighteen months previous to this study. In two other instances, from nine to eighteen months had elapsed since the penicillin reaction, and thirty-three months in two other cases. In each of these instances, however, chlorprophenpyridamine maleate was mixed with the penicillin before injection. The dose was not the usual 20 mg but twice that amount, or 40 mg, mixed with the 600,000 units of penicillin. If a series of doses of penicillin was ordered for the known reactors, they received each mixed with 40 mg chlorprophenpyridamine maleate. Among these fifteen men, two received one injection of penicillin daily for four days, three received three injections, two received two injections, and eight had one injection each, for a total of twenty-nine injections in this group.

Even though not proven penicillin-sensitive, the four indefinite reactors

*Chlorprophenpyridamine maleate as Chlor-Trimeton® Maleate Injection 100 mg/cc was furnished by George Babcock, Jr., M.D., Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

were given 40 mg chlorprophenpyridamine with each dose of penicillin they received. These four patients received five injections.

RESULTS

Most noteworthy was the fact that not one of the fifteen known reactors had any kind of reaction to penicillin administered in combination with chlorprophenpyridamine maleate. Neither did any reactions occur in the four indefinite reactors. Also, none of the 540 injections of penicillin with chlorprophenpyridamine maleate in nonreactors was followed by any kind of reaction, either local or general. It is most unusual in a series such as this not to have at least one incident to disprove the rule, but such was the case. The prophylaxis of reactions by chlorprophenpyridamine maleate was complete in both known reactors and nonreactors. No side effects attributable to the antihistamine were observed.

Among the men who received 583 injections of penicillin alone, three had angioedema and serum sickness. These were diagnosed as definite reactions to penicillin and the patients admitted to sick bay and treated for periods of five to eleven days. One of the allergic reactions occurred in a patient with severely infected bilateral dermatophytosis of the feet with lymphangitis and lymphadenitis. This man was hospitalized for six days while receiving his first three doses of penicillin. Six days after his seventh injection, given in the clinic, he was admitted with a reaction, severe angioedema He required hospitalization for nine days during which he received antihistamines and various other systemic measures for the alleviation of this allergic reaction to penicillin. Into the permanent health record of each of the three patients manifesting a reaction has been written a statement that they are never to receive penicillin alone because of severe reactivity to it.

Three other men receiving penicillin alone may have had a penicillin reaction but its occurrence was debatable. One of them had an immediate reaction—fainting, pallor, perspiration—but revived upon the administration of 1/2 cc of 1:1000 epinephrine. Another patient had a nervous reaction. Ammonia from an ampul held under his nose revived him. The third became comatose after the injection of penicillin. Checking into his history, as was done in every instance of reaction or suspected reaction to penicillin, it was found that he had had six or seven injections of penicillin spaced months or years apart and given, according to him, for an upper respiratory infection, influenza, or an early virus infection. The injections had been given by a private physician before the patient's entrance into the Marine Corps. An hour after the coma, he developed a slight maculopapular rash with a suspicion of hives. One-half cubic centimeter of 1:1000 epinephrine was administered immediately and then one 4 mg chlorprophenpyridamine maleate tablet every three hours. By the following morning he had recovered completely. It is interesting to note that this

man was classed as an indefinite reactor when he returned two months later for another penicillin injection. At that time, he received penicillin with 40 mg chlorprophenpyridamine maleate and had no vasomotor, skin, or other type of reaction.

The six reactions occurring among 583 injections of penicillin represent an incidence of 1.03 per cent in the control series. No known reactors were included in this group. This incidence of reactions is in contrast to the complete lack of reactions among 540 injections of 600,000 units penicillin combined with 20 mg chlorprophenpyridamine maleate. Contrasting with it even more sharply is the absence of reactions among fifteen known reactors receiving 40 mg chlorprophenpyridamine maleate with doses of 600,000 units of penicillin, and four indefinite reactors receiving the same amounts of each substance.

DISCUSSION

The results obtained in this study lead to the recommendation that chlorprophenpyridamine maleate injection 100 mg/cc be combined routinely with penicillin for injection whether an individual has previously received the antibiotic or not. There is no doubt of extensive abuse in the use of penicillin. Yet all of the reports and advertisements on the increasing incidence of severe reactions to penicillin will not end it. Penicillin is too good a drug to abandon its use because of the possibility of reactions. Therefore, if penicillin can be made safe for the majority of the population by the incorporation of chlorprophenpyridamine maleate in the same syringe with an aqueous penicillin preparation, then a valuable addition will have been made to every physician's armamentarium.

It would also be our suggestion, based on this study, that the medical organization of the military services be authorized to undertake a more extensive investigation of the use of chlorprophenpyridamine maleate in the prophylaxis of penicillin reactions. Then, if the extremely favorable results reported above were borne out, a recommendation could be made to the Surgeon General's office that all penicillin administered at military establishments have chlorprophenpyridamine maleate incorporated with it, or that this antihistamine in solution be available to all physicians for admixture with aqueous penicillin before injection.

SUMMARY

The possibility of sensitivity reactions to penicillin is stressed and the likelihood pointed out of preventing them by simultaneous administration of an antihistamine, chlorprophenpyridamine maleate in injectable solution. No reactions occurred among: (1) 540 injections of 600,000 units of penicillin with 20 mg chlorprophenpyridamine maleate in the same syringe in patients exhibiting no previous sensitivity to penicillin; (2) twenty-nine injections of 600,000 units of penicillin with 40 mg chlorprophenpyridamine maleate in fifteen known reactors; or (3) five injections of 600,-

000 units penicillin with 40 mg chlorprophenpyridamine maleate in four indefinite reactors. No side actions attributable to the antihistamine were noted. Three definite and three indefinite reactions occurred among 583 injections of penicillin alone in individuals not known to be sensitive to penicillin, an incidence of 1.03 per cent. The severe reactions were angioedema and serum sickness. These favorable results have led to the suggestion that chlorprophenpyridamine maleate solution be administered with each dose of penicillin for the prophylaxis of sensitivity reactions.

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FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

The Council on International Affairs of the American College of Chest Physicians announces that the Fourth International Congress on Diseases of the Chest will be held August 19-23, 1956, in Cologne, Germany. Professor Gerhard Domagk, discoverer of the sulfonamides and Nobel Prize winner, will be president of this world congress. The most recent scientific developments in pulmonary and cardiovascular disease will be discussed by eminent scientists from all over the world. The Committee on Scientific Program is now accepting abstracts of papers on original work, and these should be sent to Professor Andrew L. Banyai, Chairman, Council on International Affairs, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A. Additional information about the congress may be obtained from the Executive Offices of the College at the foregoing address in Chicago.

THE GENERAL TREATMENT OF ALLERGIC DERMATOSES

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BEFORE discussing the treatment of allergic dermatoses, there are three points which should be made clear. In the first place, such a topic must be primarily in the nature of a review rather than a report of a specific investigation. Secondly, since this represents a dermatologist's point of view, the emphasis might best be placed on topical therapy rather than on the more controversial matter of treatment directed at altering underlying immunologic or allergic mechanisms. Finally, since we are to discuss treatment of allergic dermatoses, we must dispose of the basic question of which dermatoses are to be considered as allergic. No general agreement on this point can be expected, for in the broadest sense it is difficult to conceive of inflammation existing for long without some specific alteration in capacity to react, while in the strictest sense, an inflammation of the skin based solely and entirely on an antigen-antibody reaction devoid of other factors would be unusual. I would like to include as allergic dermatoses some cases in each of the morphologic categories: eczema (including atopic dermatitis), urticaria, purpura, and erythema multiforme. Furthermore, from a standpoint of purely topical therapy, the nature of the pathogenetic mechanism is unimportant, since this treatment is symptomatic and directed against the inflammation itself rather than at its cause. However, it should not be implied that because this discussion undertakes to emphasize topical therapy, more definitive measures directed at pathogenesis are deprecated, and to avoid this possibility a sketch of therapy based on multiple factorial concepts of etiology will be included.

The basic principle that topical therapy is aimed at reducing inflammation of the skin is so elementary that its mention seems superfluous. This principle sounds simple indeed, but because of the differences in the way individuals react, as well as the differences in the way the same individual reacts at different times, the variables are compounded, and to translate our principle into action then appears to be more of an art than a science. The evaluation of the dermatologic situation in a given case depends on inspection of the whole involved integument and estimation of the intensity, extent, and acuteness of the inflammation. This evaluation and the selection of appropriate topical therapy is dependent on the experience of the therapist.

The first step in topical therapy is choosing the vehicle or the physical state which the application is to assume. These vehicles are graded against

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the degree and extent of the inflammation and appropriate selection is made. Solutions make use of water as the vehicle and are useful in general for very acute inflammatory dermatoses with or without weeping. The temperature should be cool or tepid depending on the extent of the eruption, but never either extremely hot or cold. The capillary bed, already dilated because of inflammation, is dilated further by extremes of temperature, while a cooling effect tends to cause constriction of the vessels with paling of the lesions and temporary reduction of the inflammation. Chilling is to be avoided and, if large surfaces are treated simultaneously, the temperature and time factors may become critical. The use of localized compresses, staggered compresses applied to various areas consecutively, or baths are selected according to the requirements of a given case. Some patients are admirably handled with baths repeated several times daily, others, too sick for the tub, must be handled with compresses applied to different areas for short periods. The choice of solution is made with factors of astringent, antipruritic, anti-infectious and staining qualities in mind. Aluminum acetate or subacetate is one of the very useful solutions for applications of limited extent. The dilution factor is important and ranges for the N.F. Liquor, one to sixteen or higher. The application is made for fifteen minutes or longer, and the compresses kept quite saturated lest the solution become strengthened through evaporation. In the presence of infection, compresses of potassium permanganate 1:8000, or Zephiran® 1:4000, may be more effective, and in localized inflammations with much weeping the more astringent 1:400 solution of silver nitrate may be desirable. The intense staining qualities of some of these substances are obvious disadvantages. The colloid bath lends itself well to cases of great extent. Oatmeal, cooked as for eating and with about three cups in a cheesecloth bag swished about in a tepid bath, will often prove soothing to the inflammation, anti-pruritic, and a great comfort to the patient. One package of Linit or hydrolysed starch may be substituted, and a cup of bicarbonate of soda, in addition, sometimes enhances the antipruritic effect. The commercial product derived from oatmeal, known as Aveeno,® is convenient and some patients prefer it for this reason. Sometimes wet dressings of cow's milk are well tolerated, soothing, and not so drying, but occasionally they are poorly tolerated and cause a sharp increase in the inflammation. The time spent in using solutions may vary from a few minutes daily to continuous application, depending on the patient's requirements, tolerance, and response. Lotions and liniments are suspensions that physically lie between the solutions used for compresses or baths and the more viscid creams and ointments. They are useful in many situations since they are much easier to use than compresses and baths. They vary greatly in their physical character of astringency or emollient effects according to their ingredients.

Sooner or later, treatment with compresses, baths, or shake lotions leads to excessive drying with increased itching, scaling, and fissuring, and this

effect must be overcome by the use of an emollient. Usually in the more severe inflammations an oil or grease for this purpose will be poorly tolerated, and a water miscible cream or emollient lotion is a safer choice. The time at which this change in therapy is introduced, as well as the product itself, may be very critical, and it is not unusual to see a subsiding dermatitis flare up when the use of emollients is attempted. When this occurs, the former wet therapy must be resumed and some time later another emollient tried. In such situations a paste, such as Lassar's, serves as a compromise and may be well tolerated and protective. The disadvantage is that it may dry and cake and require the addition of oil for its removal. As the inflammation subsides and becomes chronic with hyperkeratotic scale or lichenification, usually the more greasy the preparation the more effective it is and the better it is tolerated subjectively. After the more acute phase has been brought under control with solutions to a point where an emollient vehicle is tolerated, it is time for consideration of what medicaments may be added to the vehicle and for what purpose. In this stage we consider in addition to the reduction of the inflammation, the control of pruritus and infection through topical medications, a number of which are worthy of specific reference.

Tars are of such variety in source, composition, physical character and effect, that it is impossible to consider more than a few examples. The addition of a prepared tar to a bath is sometimes effective in relieving pruritus. Applied in ointment form to localized areas of chronic inflammation, tars may relieve itching and stimulate the reduction of inflammation as well. In using tars it is well to apply the old adage that it is better to know a few products well than to attempt to grasp the use of a wide variety of substances.

Of topical medicaments that control surface infection, ammoniated mercury is a time-honored remedy. Because of the occasional sensitizing effect of the mercury, as well as the greater effectiveness of some of the newer preparations, the use of this substance is on the wane. Vioform® in a strength of one to three per cent put into a base of cream, paste, or ointment is very effective and rarely sensitizing. Many antibiotics alone or in combinations are useful. Penicillin is avoided because of a rather high sensitizing potential when used topically, which then destroys its possible future usefulness as a systemic antibiotic in these individuals. For similar reasons, sulfonamides are avoided for topical therapy, although there appears to be an exception in sulfacetamide, now rather widely used in topical therapy with little sensitization reported as yet.

Antihistaminics have been incorporated in topical preparations to relieve itching and inflammation, but it has been shown that any effect is equivalent to that of a topical anesthetic and the sensitizing potential is so great that their use has been greatly reduced by most dermatologists.

Anesthetic substances have been used, but again the sensitizing potential is a serious drawback. We see very intense allergic contact type dermatitis

with extensive "id" eruptions from such ointments as Nupercainal® and Americaine®. Quotane® and Tronothane® are newer preparations without the "caine" radical, and so far seem safer.

Traditionally, we must include phenol in one-half to one per cent, and menthol in one-fourth to one-half per cent. These are still useful at times, but not strikingly effective, and newer more effective preparations are replacing them.

Topical steroid therapy has lately become the subject of such interest that we could devote our entire attention to this subject. The relative merits of Hydrocortone® Acetate and Fluorohydrocortisone Acetate in various strengths and vehicles, alone and in combination with antibiotics, is a subject currently in the limelight. I can only agree that these substances are effective in reducing inflammation in many dermatologic situations. In the more extensive cases the cost and the possibility of absorption with systemic effect from the Fluorohydrocortisone become important. Effective as these substances often are, their use is disappointing if not combined with the principles of topical therapy previously mentioned, as well as those factors of etiology yet to be considered.

A multiple factorial concept of pathogenesis and treatment is equivalent to the old adage that the patient should be treated rather than his disease. Critical evaluation of each patient from a standpoint of multiple etiologic factors applies to individuals presenting allergic dermatoses as well as other diseases, and no therapy is really complete without an attempt at delineating and excluding causative factors. In keeping with the stated limitations of this discussion, these will only be outlined.

A. Psychogenic factors are always present to some extent. Unless severe and requiring psychiatric help, these may be handled by reassurance, sedation, and direction of the patient's activities and emotional reactions. Currently, the rauwolfia derivatives and Thorazine® are being investigated for their tranquilizing effects, but the barbiturates, chloral hydrate, and bromides are still of value.

B. General health and metabolic factors include the detection and correction of anemia, diabetes, hypothyroidism, obesity, stasis, and dietary habits. These may seem too obvious to mention, but it might be emphasized that paroxysms of itching with scratching and exacerbation of the eruption is sometimes caused by overeating, alcoholic intake, or overstimulation by coffee. At times, a patient who is run down and tired is benefited by a high vitamin intake with an apparent improvement in response to other therapy. Further, the administration of calcium orally or intravenously does appear to be of benefit in some cases.

C. Factors of primarily irritating contacts are numerous; scratching, soap and water, rough clothing, temperature, climatic factors, and the possibility of overtreatment must all be considered, and success of other treatment may depend on eliminating one critical factor.

D. Local infection is sometimes a secondary factor in allergic dermatoses, and in the case of infectious eczematoid dermatitis there is presumed to be a local allergic reaction to the bacterial flora on the skin. In such cases, emphasis on overcoming local infection is rational, and striking results are occasionally seen from this therapeutic approach.

E. Allergic factors may be identified in different ways. By and large, dermatologists put more emphasis on history and less on testing, at least as far as immediate wheal sensitivities are concerned. Patch tests and the test of elimination and re-exposure are used extensively. These allergic factors include:

1. Contact allergens such as detergents, chemicals, plants, cosmetics, medicaments, and surface bacteria.
2. Endogenous allergens such as those produced in foci of infection and the autosensitization "eczematid" concept.
3. Environmental inhalant allergens such as pollens, house dust, and dander.
4. Ingested allergens as foods, drugs, and contaminants.

When allergens cannot be avoided, internal therapy directed at blocking the pathogenetic mechanisms includes many things. The use of antihistamines has been disappointing except in certain cases of urticaria. The internal use of steroids is falling into disfavor in cases which may run a prolonged course, unless the condition is very severe. We are reluctant to start steroids on a case of atopic eczema, for example, since increasing doses for indefinite periods may be required and serious late effects encountered. The internal administration of antibiotics for the elimination of focal infections not amenable to surgical treatment is rational therapy, as are attempts at desensitization through vaccines or more specific proteins or polysaccharides, although from a practical standpoint these are less apt to be effective.

SUMMARY

While evaluation of multiple etiologic factors in the production of an allergic dermatitis should be made as a guide to rational internal therapy, topical therapy may meanwhile be undertaken and may be critical in the progress of the case. In topical therapy the principle of reducing inflammation is placed first, while the elimination or reduction of infection and pruritus is of secondary importance.

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A METHOD OF ESTIMATING PULMONARY DISEASE FROM INSPIRATION AND EXPIRATION ROENTGENOGRAMS OF THE LUNGS: ITS APPLICATION TO THE EVALUATION OF EMPHYSEMA

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AN accurate roentgenogram evaluation of pulmonary emphysema in the early stages by classic procedures is difficult or impossible. Ordinary roentgenograms give dependable information only in the advanced stages of the disease; further, a correct interpretation of the films is often uncertain. There may be different opinions by different observers or even by the same observer at different times. It seemed to the author, therefore, that some method which would permit the detection of emphysema in the early stages, yet would be comparatively simple to execute, was eminently desirable. A technique fulfilling these requirements, developed from studies of 264 cases, is presented here.

Pulmonary emphysema is a pathologic condition in which the lungs lose to some extent their capacity to expand and contract because of overinflation of the alveoli and loss of elastic fibers. The breathing pattern tends to become predominantly thoracic. It is in the early stages of emphysema that therapeutic attack is most important, and a numerical guide to gauge its degree and the response to treatment is most useful.

In approaching this problem, it was believed that an accurate and permanent record of ventilatory function could be obtained by combining the fluoroscopic and roentgenographic data, and that this, in turn, would be possible by comparisons of films made on both inspiration and expiration. To establish a breathing pattern (thoracic or diaphragmatic), it would be necessary to determine changes in the upper and lower areas of the lungs, since changes in the upper area are governed by thoracic movement and changes in the lower area are governed chiefly by diaphragmatic movement.

With these ideas in mind, posterior-anterior and lateral films of the chest were made on inspiration and expiration. A posterior-anterior film was first made after full inspiration. Then, after simple expiration, as complete as possible, the patient was asked to hum in order to expel additional air, and another roentgenogram was made while the lungs remained in this contracted state. In the same manner, inspiration and expiration films were made in the lateral projection. The humming contracts the chest more than simple expiration.

On each of the posterior-anterior films horizontal lines were drawn

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through the apices of the lungs and between the costophrenic angles. Vertical lines were drawn through the mid-portion of the lung fields between the upper and lower horizontal lines. Another vertical line was

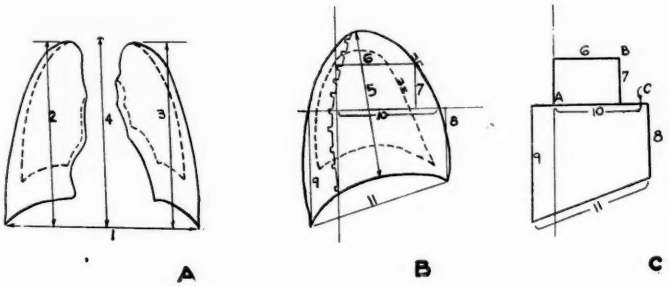

Fig. 1. (a) Pantographic tracing of roentgenograms of the chest on inspiration and expiration, posterior-anterior view. (b) Pantographic tracing of roentgenograms of the chest on inspiration and expiration, lateral view. (c) Diagram of upper and lower compartments of the lungs, lateral view.

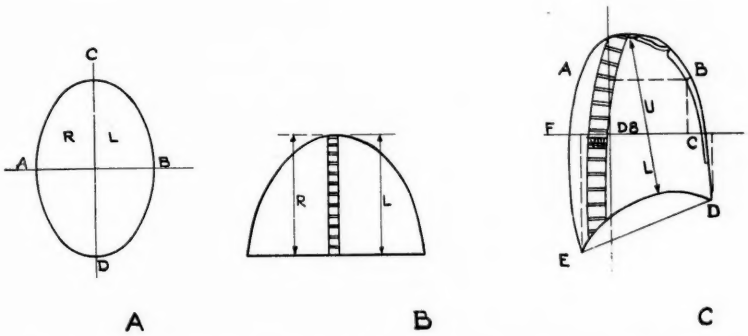

Fig. 2. (a) Area of an ellipse = AB x CD x .7854. (b) Calculations of areas of chest on posterior-anterior films: Area of 2R = Rt. vertical x 2 x base x .7854 or Rt. vertical x base x .3927. (c) Calculations of compartment areas of chest on lateral films: Area of U = AB x BC; Area of L = 1/2 (FE plus CD) x D8AP.

drawn from the tip of the spinous process of the first thoracic vertebra to the lower horizontal line (Fig. 1a). On each of the lateral films the upper anterior margin of the eighth dorsal vertebra was marked and, with this as a point of origin, as abscissa and ordinate, or both horizontal and vertical lines, were drawn, dividing the chest into upper and lower compartments (Fig. 1, b and c). It is best to draw the co-ordinates on the full inspiration film first. Vertical wax pencil marks are made at the anterior margins of a vertebral body above and below the point of origin of the co-ordinate. The point of origin is marked on the expiration film and the wax pencil marks are made on the vertebral bodies corresponding to those made on inspiration films. One should superimpose the expiration

TABLE I. DIAMETERS OF THE THORAX

Posterior-Anterior Views:

1. Distance between costophrenic angles (base).
2. Distance between apex of lung and base line (right).
3. Distance between apex of lung and base line (left).
4. Distance between tip of spinous process of first thoracic vertebra and base line (costophrenic angle shift).

Lateral Views:

5. Distance from apex of dome of diaphragm to lung apex (total height).
6. Distance from ordinate to junction of body with manubrium of sternum (upper AP).
7. Distance from abscissa to junction of body with manubrium of sternum (upper vertical).
8. Distance from anterior costophrenic angle to abscissa (AV).
9. Distance from posterior costophrenic angle to abscissa (PV).
10. Distance from upper anterior margin of eighth dorsal vertebra along abscissa to sternum (D8AP).
11. Distance between anterior and posterior costophrenic angles:
    Point A = Upper anterior margin of eighth dorsal vertebra.
    Point B = Junction of body with manubrium of sternum.
    Point C = Intersection of abscissa and sternum.

TABLE II. SIGNIFICANCE OF CHANGES IN DIAMETERS OF THORAX

I. Movement of ribs and sternum:
   1. Upper area %, lateral film.
   2. Index of costal efficiency (I.C.E.)—Upper vertical % change plus upper vertical cms. change x 10, lateral film.
   3. Upper vertical %, lateral film.
   4. D8AP % (AP diameter of chest at level of upper border of D8), lateral film.
   5. Base %, posterior-anterior film.

II. Movement of diaphragm:
   1. Costophrenic angle shift % and cms. (vertical movement of costophrenic angles), posterior-anterior film.
   3. Posterior vertical % and cms., lateral film.
   4. Anterior vertical % and cms., lateral film.
   5. Index of diaphragmatic efficiency (I.D.E.) = The sum of costophrenic angle and posterior and anterior vertical % change, plus the sum of costophrenic angle and posterior and anterior vertical cms. change x 10, posterior-anterior and lateral films.
   6. Total height, posterior-anterior and lateral films.

III. Combined rib and diaphragm movement:
   1. Anterior area %, posterior-anterior film.
   2. Lower area % (chiefly diaphragm, but modified by D8AP diameter), lateral film.
   3. Total area change, posterior-anterior and lateral films.
   4. Vital capacity and maximum breathing capacity, spirometer.

film on the inspiration film and make the points of origin and the wax pencil marks coincide, then mark the co-ordinates on the expiration film. This is very important, since rotation of the expiration film about the point of origin vitiates the measurements. With these co-ordinates, multiple standard measurements were made, as shown in Table I. This table defines the diameters of the thorax, while Table II indicates the significance of the changes in the diameters.

On the posterior-anterior films, areas of the lungs on inspiration after the humming procedure were computed by multiplying the vertical by the

horizontal measurement and the result by .392 (Fig. 2, a and b). The ratio residual area (RA) to total lung area (TLA) was then determined by dividing the RA by the TLA.

The upper and lower areas were computed separately on the lateral films. The rectangular upper area lies between the abscissa and the ordi-

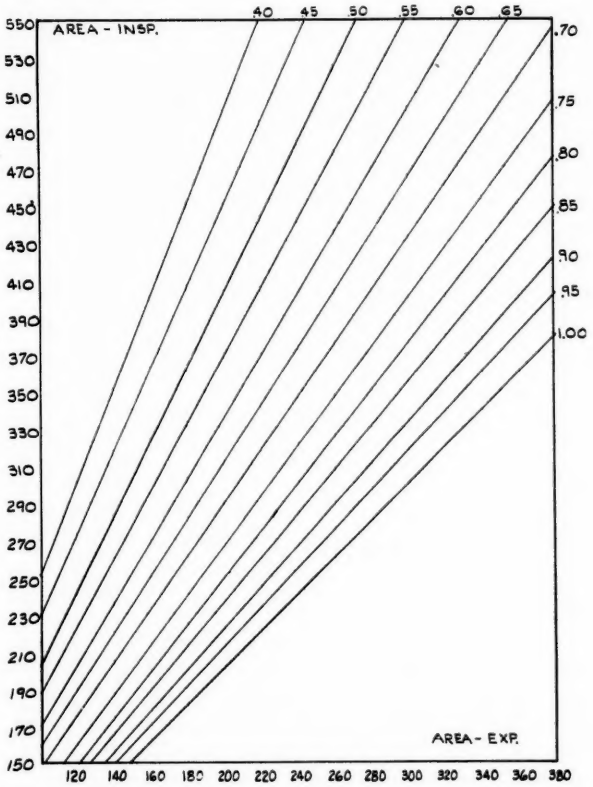

Fig. 3. Graph for computing ratio of residual area to total lung area, posterior-anterior film.

nate, the upper anterior corner of the rectangle being the junction of the body and the manubrium of the sternum. The lower area is a trapezoid lying between the abscissa and the ordinate, the lower corners of which are formed by the anterior and posterior costophrenic angles (Fig. 2c). The upper and lower areas were added and the ratio of residual area to total lung area was determined by dividing the sum of these areas on the inspiration film into their sum on the expiration film.

The author has evolved a graph for determining the ratios (Fig. 3).

TABLE III. VENTILATORY GRADES OF MEN

Grade	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
PA RV/TLC	40	43	47	50	53	57	60	63	67	70	73	77	80	83	87	90	93	97
Up. Area %	174	173	171	169	164	159	155	146	137	129	116	103	90	80	70	59	50	41
ICE	180	174	168	163	157	151	145	139	134	129	123	118	113	107	102	97	91	86
UP. Vert. %	147	140	133	126	119	112	105	98	91	85	78	71	64	57	50	43	36	29
D8AP %	43	40	38	35	33	30	28	26	24	22	20	18	15	13	10	8	6	4
Lat. Base %	29	27	25	22	20	18	15	13	10	8	6	4	0	0	0	0	0	0
Cp. %	52	49	45	42	39	36	33	30	27	24	21	18	15	13	11	10	8	7
Cp. cms.	12	11.3	10.6	10	9.3	8.6	8	7.3	6.6	6	5.3	4.6	4	3.3	2.6	2.0	1.3	.6
PV %	116	108	100	93	85	77	69	61	53	46	38	30	23	16	8	0	0	0
PV cms.	9.0	8.5	8	7.6	7.1	6.6	6.1	5.7	5.3	4.9	4.4	4.0	3.6	3.2	2.8	2.4	2.0	1.6
AV %	88	84	80	77	74	70	66	60	54	49	39	29	19	10	1	−8	−16	−23
AV cms.	3.4	3.2	3.0	2.9	2.7	2.5	2.4	2.2	2.0	1.8	1.6	1.4	1.2	1.1	1.0	−9	−8	−7.5
IDE Total	533	503	473	444	414	384	354	228	202	275	246	218	190	150	110	70	30	0
IDE cms.	26.5	25.3	23.1	22.0	20.5	19.0	17.5	16.2	15.0	13.7	12.3	11.0	9.6	7.6	5.6	3.6	2.4	1.2
IDE %	268	253	238	223	208	193	178	164	151	137	122	108	93	73	53	33	19	5
Total Ht. %	73	68	62	57	52	48	43	38	32	27	22	17	12	9	7	4	2	0
Ant. Area %	93	87	81	75	69	63	57	51	46	40	34	28	22	16	11	5	0	0
Low. Area %	155	148	142	136	130	124	118	111	105	99	89	80	71	53	35	17	0	0
Tot. cms. 2	312	309	305	301	289	277	265	249	234	219	200	181	162	147	131	116	100	84
MBC %	26	25	24	22.9	22.5	22.1	21.7	21.5	21.3	21.1	20.7	20.3	19.9	18.7	17.6	16.5	15.4	14.3
VC % (50−)	128	127	126	125	123	122	121	115	108	102	95	87	79	71	64	57	50	43
Lat. RV/TLC	28	32	36	40	44	48	51	55	59	62	66	70	74	78	81	85	89	93
VC (50+)	122	119	117	115	111	106	101	95	89	83	79	72	67	61	54	47	40	33

TABLE IV. VENTILATORY GRADES OF WOMEN

Grade	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
PARV/TLC	40	43	46	50	53	56	60	63	66	70	73	76	80	83	86	90	93	96
Up. Area %	108	107	106	105	104	102	100	97	94	91	83	76	69	55	42	29	0	0
ICE	135	134	132	130	128	126	124	120	116	112	103	95	87	73	58	43	20	13
Up. Vert. %	124	117	109	101	94	87	80	76	72	68	58	47	36	29	22	15	8	1
D8AP %	42	40	38	35	32	30	28	25	23	21	18	16	14	11	9	7	5	3
Lat. Base %									10									
Cp. %	52	47	44	41	37	34	31	27	24	21	17	14	11	7	4	1	0	0
Cp. cms.	9.8	9.3	8.8	8.3	7.9	7.2	6.7	6.1	5.6	5.1	4.5	4.0	3.5	3.0	2.4	1.8	1.2	.6
PV %	110	103	96	89	83	76	69	61	54	47	41	34	27	20	13	6	0	0
PV cms.	9.4	8.9	8.4	7.9	7.3	6.8	6.3	5.8	5.2	4.6	4.1	3.5	2.9	2.3	1.8	1.3	.7	.2
AV %	123	114	105	96	77	78	70	61	53	45	37	28	19	7	−5	−17	−29	−
AV cms.	5.4	5.0	4.6	4.2	3.9	3.5	3.1	2.7	2.3	1.9	1.5	1.1	.7	.1	−.4	−.9	−1.3	−1.7
IDE Total	478	450	421	392	362	333	304	274	243	212	178	150	122	94	64	37	9	0
IDE cms.	23.3	21.9	20.5	19.1	17.7	16.4	15.1	13.7	12.2	10.7	9.2	7.8	6.4	5.1	3.7	2.3	.9	0
IDE %	245	231	216	201	185	169	153	137	121	105	86	72	58	43	27	11	0	0
Tot. Ht. %	67	63	59	55	51	47	43	39	35	31	27	23	19	16	12	8	4	0
Ant. Area %	97	91	84	77	71	64	58	51	45	39	32	25	19	12	6	0	0	0
Low. Area %	233	218	203	189	174	159	145	129	114	99	83	68	53	37	23	9	0	0
Tot. cms.	312	295	278	261	243	226	209	191	174	157	140	123	106	89	72	55	38	21
MBC %	369	352	335	319	303	287	271	255	339	223	206	190	174	158	143	128	113	98
VC % (50−)	146	141	136	131	125	120	115	111	106	101	95	90	85	80	76	71	66	61
Lat. RV/TLC	30	33	37	40	43	47	50	53	57	60	63	67	70	73	77	80	83	87
VC (50+)	131	125	119	114	108	102	97	91	86	81	75	70	64	58	52	47	42	36

A work sheet for record and to facilitate calculations is illustrated (Fig. 4).

In this study both normal and abnormal cases were reviewed and ratios were determined for each. The lowest ratio was .40 and the highest 1.00.

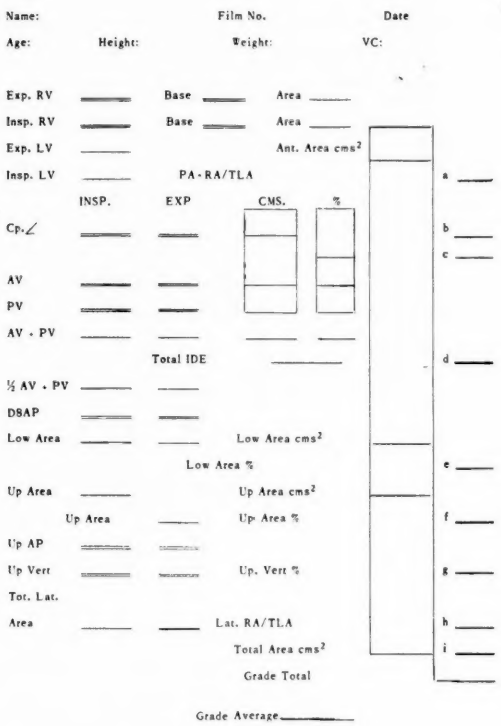

Fig. 4. Work Sheet.

These were divided into eighteen groups, representing ventilatory grades. Absolute and percentage changes in the standard chest measurements were determined and tabulated separately for men and women. A general average of each measurement for each of the eighteen ventilatory grades (ratio groups) was reached by adding the measurements for each grade separately and dividing the totals by the number of individuals with that ventilatory grade (Tables III and IV). From a correlation with the clinical findings, it was discovered that grades 40 to 70 were consistent with normal ventilation, while those from 70 to 100 indicated corresponding degrees of ventilatory insufficiency. Interval examinations also showed a close parallel between the average grade and the clinical course of the

patient. The lateral films offered an excellent indication of the predominance of the thoracic or diaphragmatic components of pulmonary ventilation. Moreover, the results could be reproduced with remarkable accuracy, even when the radiographic studies were made by different technicians in different hospitals and clinics.

The ventilatory grade was determined in thirty-five unselected cases, without inclusion of vital capacity and maximum breathing capacity values. The average ventilatory grade for all values proved to be 12.235, and for roentgen values alone, 12.243. These findings indicate that spirometry is unnecessary in conjunction with this radiologic method for determining ventilatory grades.

After it was found that the lung areas could be computed mathematically, it was believed that vital capacities could be rather accurately estimated by this technique. It did not seem necessary to use the planimeter, over-size view box and spirometric studies as employed by Cobb and others. Vital capacity measurements had already been made on all the 264 patients in this series. Sixty-nine consecutive patients, with both normal and abnormal lungs, were chosen for study. The posterior-anterior diameter of the chest was multiplied by the frontal area to obtain the chest volume. The posterior-anterior and lateral inspiration films provided an index of the total lung capacity, while the posterior-anterior and lateral expiration films gave an index of residual volume. From this the ratio of residual volume (RV) to total lung capacity (TLC) was established. For comparative purposes, residual volume values were then estimated on the same sixty-nine patients by Cobb's method, that is, by subtracting the spirometric vital capacity from the total lung capacity. The results from the two methods were as follows:

Index of TLC (x-ray): 8876 cc
Index of RV (x-ray): 5850 cc
Index of RV (TLC minus spirometric VC, Cobb method): 5941 cc
V/C (x-ray): 3926 cc
V/C (Spirometer): 3115 cc
RV/TLC (x-ray): .66
RV/TLC (Cobb method): .65

Although the vital capacities determined radiologically compared closely with those obtained spirometrically, the total lung capacities and residual volumes were high, the volume of the heart and mediastinal structures and the volume below the curvature of the diaphragm having been included.

The classical signs of pulmonary emphysema in conventional posterior-anterior and lateral films of the chest are as follows: (1) Widening of the intercostal spaces; (2) horizontal direction of the posterior portions of the ribs; (3) larger and better illuminated retrosternal space as seen in

the lateral projection; (4) depressed, flattened diaphragm; (5) blunting of the costophrenic sinuses; (6) increased radiolucency of the lung fields; and (7) meager lung pattern.

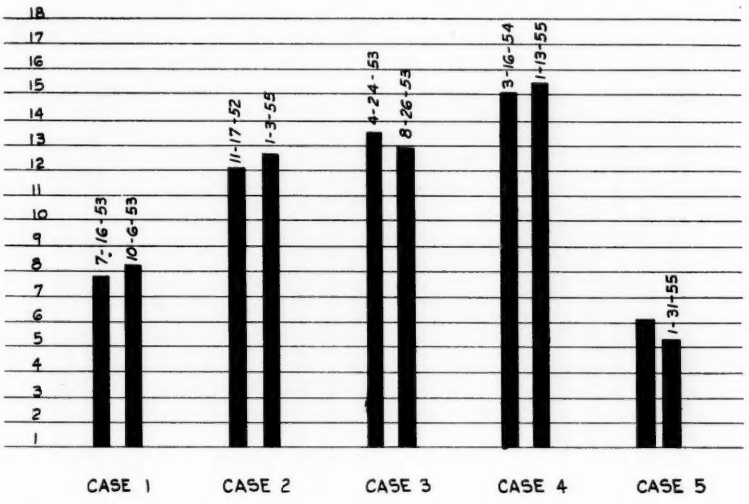

Fig. 5. Graphs showing reproducibility of the measurements of ventilatory function on successive examinations by the technique described.

If posterior-anterior projections in full inspiration and full expiration are made, the following signs are also observed: (1) Decreased respiratory movement of the diaphragm; (2) increased contrast of the hilar shadows against the lighter lung fields; and (3) decrease in difference of illumination of the lungs on inspiration and expiration.

In the interpretation of these changes, several points are worthy of note.

As emphysema becomes advanced, the movement of the diaphragm may be reversed; that is, may move upward on inspiration and downward on expiration. In this study, it was found that the most sensitive place to measure this paradoxical movement is the anterior part of the diaphragm. The movement is seldom apparent in the posterior portion except in the latest stages of emphysema.

Some investigators say that women are thoracic breathers and men are diaphragmatic breathers.[4] The author has observed no significant difference in this respect between the sexes. In normal chests of nineteen men and sixteen women, the ratio of lateral upper area change was .516 in men and .554 in women.

An estimate of lung densities from ordinary roentgenograms is subject to error, in that variations from the normal may be due either to changes

in the lung itself or to differences of anterior-posterior diameter (hypersthenic or asthenic), or to variations in thickness of the overlying soft tissue.[2] Some error may arise from the fact that the emphysema, and con-

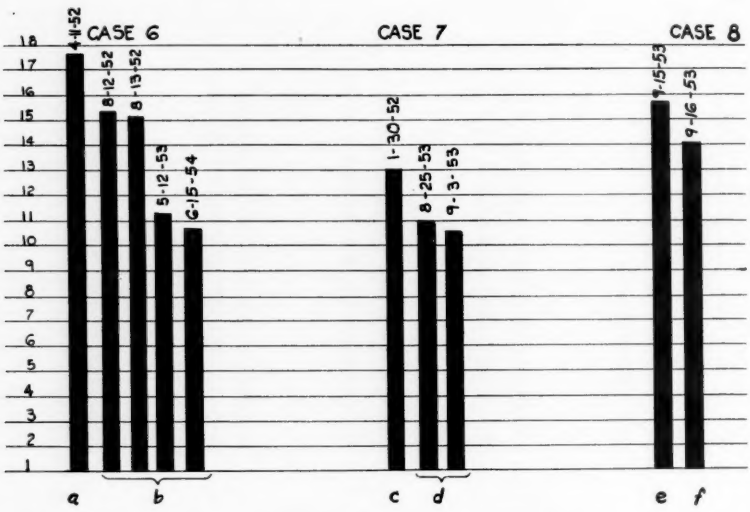

Fig. 6. Graphs showing ventilatory function before and after treatment. *Case 6.*—(a) Before treatment. (b) Emphysema belt and breathing exercises. *Case 7.*—(c) Before treatment. (d) After treatment with ephedrine, nembutal and aminophyllin. *Case 8.*—(e) Before treatment. (f) Twenty minutes after aminophyllin.

sequently the radiability, may be masked by an associated condition, such as fibrosis, polycythemia, increased viscosity and congestive failure.[5] With this method, errors in estimating densities are minimized, since the change observed between the inspiration and expiration is of chief importance.

The ratio of RA/TLA may be elevated because of a decrease in the excursion of the diaphragm due to pain, dyspnea, muscular weakness, chest binders or a previous operation, any of which may prevent fullest inspiration, an elevated ratio is not necessarily indicative of emphysema, although in emphysema the ratio is invariably elevated.[3]

It is possible that the method described may likewise be employed in certain other conditions, such as pleural adhesions, poliomyelitis, myesthenia gravis and edema and passive congestion of the lungs, for demonstrating changes in ventilatory function not discernible by the usual procedures.

The reproducibility of the measurements of ventilatory function on successive examinations with this technique is illustrated by the graphs in Figure 5. The graphs in Figure 6 demonstrate ventilatory function before and after treatment.

SUMMARY

The author has made a study of roentgenograms of both normal and abnormal lungs in 264 individuals, with the idea of developing a simple method of estimating the degree of pulmonary expansion and contraction and demonstrating abnormal breathing patterns in the early stages of emphysema. These objectives have been fulfilled in a technique presented here, which involves the use of standard measurements of posterior-anterior and lateral films of the chest on full inspiration and full expiration, and an estimate of the ratios of the residual area to total lung area.

This method has also proved useful for estimating vital capacities of the lungs. Values obtained by radiologic measurements compared closely with those obtained spirometrically.

The advantages of the method may be summarized as follows:

1. It affords an accurate basic roentgen examination of the lungs.
2. It permits early recognition of disordered breathing patterns.
3. It permits an estimation of the ratio of the total lung capacity to residual volume.
4. It permits a radiographic estimation of vital capacity.
5. It provides a guide to the evaluation of the results of treatment.
6. It provides a permanent numerical and pictorial record of the progress of the patient.

NOTE

The author wishes to acknowledge his indebtedness to Drs. Homer E. Prince, Paul V. Ledbetter and Edwin J. Morrow for their co-operation in referring the majority of the patients included in this study.

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C-REACTIVE PROTEIN IN BRONCHIAL ASTHMATIC PATIENTS

II. Further Evaluation

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IN A previous report,[4] data obtained from the results of C-reactive protein (CRP) determinations and of antistreptolysin O (ASO) titers in 101 patients suffering from bronchial asthma were presented. We concluded that the presence of CRP in the serum of the asthmatic patient would seem to indicate the possibility of an infectious allergic process, especially if there was a recent history of symptoms resembling an upper respiratory infection associated with the asthma. The results of ASO determinations were so diversified as to preclude their usefulness as an accurate measure of infection in bronchial asthma.

The present report concerns itself with further observations in 304 patients with bronchial asthma, of which 103 were adults and 201 children up to the age of fourteen years. In addition, a control group of forty-three non-allergic children with recent upper respiratory tract infections were tested for the presence of C-reactive protein. We concentrated primarily on the pediatric group, in which we had to contend with fewer permanent changes in the bronchial structure caused by long-standing infectious processes and anatomic disturbances due to emphysema, bronchiectasis, et cetera.

The significance and occurrence of C-reactive protein was reviewed in our first report.[4] Since this report was written we have found additional references to the applicability of CRP determinations in a variety of conditions.[3,5,7-10]

METHOD

Because of the undesirability of repeated venipunctures to obtain blood for testing, we used a finger tip technique,[1] using capillary tubes with an outer diameter of at least 1.4 mm and about 90 mm in length. CRP antiserum* is drawn into a finer capillary tube with an outside diameter up to 1.1 mm, and carefully placed in contact with the patient's serum in the wider capillary tube. The test is then completed by the standard procedure. When antistreptolysin O titers are also to be determined, a

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*Schieffelin & Company, New York.

TABLE I. INCIDENCE OF POSITIVE CRP AND ASO TITERS IN CHILDREN WITH BRONCHIAL ASTHMA

Type of Asthma		No. Pts.	CRP		% Pos. CRP.	No. Pts.	ASO**		% Pos. ASO
			Neg.	Pos.			Neg.	Pos.	
Non-atopic or Infectious	Recent URI	8	1	7	87.5	4	2	2	50
	No recent URI	7	7	0	0	7	7	0	0
Atopic	Recent URI	44	42	2	4.5	38	31	7	18
	No recent URI	78	77	1	1.3	65	59	6	9.2
Mixed	Recent URI	29	24	5	16	29	20	9	31
	No Recent URI	35	35	0	0	30	27	3	10
Total		201				173			
Control Group*		43	43	0	0				

*Non-allergic, non-asthmatic children, with recent URI
**Negative = less than 166 Todd units
Positive = 166 Todd units or more

larger capillary tube is used (outside diameter 3 mm, and about 90 mm in length), and the test performed according to the established method of Rantz and Randall,[6] omitting the 1:10 dilution of the serum.

The patients were classified, on the basis of prolonged clinical observations, into three subdivisions for clinical bronchial asthma: (1) Non-atopic or infectious (negative skin test group); (2) atopic (positive whealing reactors); and (3) mixed (atopic with superimposed infection). Each group was studied in relation to whether or not they had had symptoms of recent upper respiratory infection.

Many of the children with positive CRP's were examined fluoroscopically, and in each case no infiltrations were noted.

When the CRP reactions were read, any amount of precipitation that could be seen with the naked eye was considered positive. The ASO titers were expressed as Todd units, and only those sera that showed 166 such units or more were called positive, while those that showed less than 166 units were listed as negative.

RESULTS AND DISCUSSION

Table I summarizes the results obtained with CRP and ASO determinations in 201 children with asthma and forty-three controls. In the group of patients with infectious asthma, of eight children who had suffered a recent upper respiratory infection, seven (87 per cent) yielded a positive CRP, while two of four such children showed ASO titers of 166 Todd units or more. In the same group, seven children were studied who had not had a recent upper respiratory tract infection. None gave a positive CRP or an ASO titer of 166 Todd units.

In the group of patients with atopic asthma, different results were obtained. Of forty-four patients with recent upper respiratory tract infections, forty-two were negative, and two were positive for CRP (4.5 per cent), while seven of thirty-eight patients with recent upper respi-

TABLE II. INCIDENCE OF POSITIVE CRP AND ASO TITERS IN ADULTS WITH BRONCHIAL ASTHMA

Type of Asthma		No. Pts.	CRP		% Pos. CRP	No. Pts.	ASO*		% Pos. ASO
			Neg.	Pos.			Neg.	Pos.	
Non-atopic or Infectious	Recent URI	8	5	3	37.5	8	8	0	0
	No recent URI	26	24	2	8	24	24	0	0
Atopic	Recent URI	8	6	2	25	8	6	2	25
	No recent URI	19	19	0	0	19	18	1	5.2
Mixed	Recent URI	17	7	10	58.8	15	10	5	33.3
	No recent URI	25	23	2	8	25	21	4	16
Total		103				99			

*Neg. = less than 166 Todd units.
Pos. = 166 Todd units or more.

ratory tract infection showed an ASO titer of 166 Todd units or more. In those without recent infections of the upper respiratory tract, seventy-seven of seventy-eight patients were negative for CRP and only one (1.3 per cent) was positive, whereas six of sixty-five patients without recent infections of the upper respiratory tract (9.2 per cent) gave ASO titers of 166 Todd units or more. All patients with high ASO titers in this group were negative for CRP.

In the mixed group, of twenty-nine children with recent upper respiratory tract infections, five (16 per cent) showed a positive CRP, while nine of twenty-nine (31 per cent) such children showed an ASO titer of 166 Todd units or more. All of thirty-five patients in the mixed group, who had had no recent upper respiratory infection, were negative, and only three such patients had an ASO titer above the baseline of 166 Todd units.

An additional control group of forty-three children with no history of allergy or bronchial asthma, who had had an upper respiratory infection within a week before they were tested, was studied. As far as could be determined, none of these children had had any specific therapy. All of them gave a negative CRP.

The fact that CRP appeared in the sera of such a high proportion (seven of eight) of the children with infectious asthma, who contracted an upper respiratory infection, and failed to appear in any of the non-asthmatic children who developed upper respiratory infections, as well as in almost all of the asthmatic children who did not develop upper respiratory infection (119 of 120), or in those asthmatic patients with the atopic type who did develop upper respiratory infection (forty-two of forty-four), points to bacterial sensitization as an explanation for the appearance of CRP in the infectious asthma group of children. These results suggest that the occurrence of a positive CRP following an upper respiratory infection may be of importance in the diagnosis of an infectious factor in the asthmatic child.

Table II shows the incidence of positive CRP and ASO titers in adults

TABLE III. SUMMARY OF POSITIVE CRP IN EACH CLINICAL TYPE OF BRONCHIAL ASTHMA

	Children		% Pos.	Adults		% Pos.
	No.	No. Pos.		No.	No. Pos.	
Infectious	15	7	46.6	34	5	15
Atopic	122	3	2.4	27	2	7.4
Mixed	64	5	7.7	42	12	28.5

with bronchial asthma. One hundred and three of them were tested for CRP, and, of these, ninety-nine were tested for ASO titers. Of eight patients with infectious asthma with recent infection of the upper respiratory tract, three (37.5 per cent) showed positive CRP, while none had an ASO titer of 166 Todd units or more. Of twenty-six patients with infectious asthma and without a history of recent upper respiratory tract infection, two (8 per cent) were positive for CRP, and none showed an ASO titer of as high as 166 Todd units.

In the atopic group, of eight patients with recent upper respiratory infections, two (25 per cent) were positive for CRP, and two gave ASO titers of 166 Todd units or higher. (One patient gave both positive CRP and ASO). In those without a recent upper respiratory tract infection, none showed CRP and only one of nineteen (5.2 per cent) showed an elevated ASO titer.

In the mixed group, we see a rather marked difference in the CRP figures from the adults as compared to those from the children. Of seventeen adults with recent upper respiratory infections, ten (58.8 per cent) were positive for CRP, while of twenty-five without a recent upper respiratory tract infection two (8 per cent) were positive for CRP.

The results obtained in Table II reveal that an upper respiratory infection plays a role in the production of CRP in adult asthmatic patients. Of the thirty-three patients (46 per cent) with a recent upper respiratory infection, fifteen showed a positive CRP, while of seventy patients without a recent upper respiratory infection, four (6 per cent) showed this abnormal protein.

It is very difficult to classify asthmatic adult patients, and to rule out other factors of inflammation. However, in the presence of a positive CRP in an asthmatic adult, the possibility of a bacterial sensitization should be considered after other causes for the presence of CRP have been ruled out.

No correlation was noted between the patients with positive CRP's and those who had ASO titers of 166 Todd units or more.

Table III summarizes the results obtained in children and adults without regard to recent upper respiratory tract infections. This table reveals at least a relative difference in the incidence of CRP between the children's and the adult's group. In the infectious group, 46.6 per cent

TABLE IV. INCIDENCE OF CRP IN ASTHMATIC PATIENTS

	With URI	Without URI	Controls
Children	14 of 81 (17.3%)	1 of 120 (0.8%)	0 of 43
Adults	15 of 33 (45.5%)	4 of 70 (5.7%)	
Total	29 of 114 (25%)	5 of 190 (2.6%)	0 of 43

of the children were positive for CRP as compared to only 15 per cent of the adults. In the mixed group, where the adults have had a longer time to develop inflammatory changes, 28.5 per cent of forty-two adults, and only 7.7 per cent of sixty-four children gave positive CRP. In the atopic group, only 7.4 per cent of the adults and 2.4 per cent of the children were positive for CRP. These latter figures could well parallel the results one might expect to find in the general population without regard to atopic bronchial asthma.[2]

Table IV summarizes the effects of upper respiratory infections on CRP in all patients with bronchial asthma. In children, the incidence of CRP was about twenty-two times greater in those with upper respiratory infections (17.3 per cent) than in those without it (0.8 per cent). In adults, the incidence was about eight times greater in those with upper respiratory tract infections (45.5 per cent) than in those without it (5.7 per cent). The total incidence in both groups was about ten times greater in patients with upper respiratory infection (25 per cent) than in those without it (2.6 per cent). In the control group of children, no positive CRP was obtained. Adults with recent upper respiratory infection, without a history of asthma, were not used as controls, because it was felt that too many complicating conditions that might produce CRP were possible in this group. The results show that upper respiratory infections play an important role in producing an abnormal blood protein, CRP, in patients with bronchial asthma, clinically classified as infectious or of mixed etiology.

SUMMARY

1. A survey of C-reactive protein and antistreptolysin O titers in 304 patients with bronchial asthma, and forty-three control patients, has been made.

2. In asthmatic patients classified as "infectious," the occurrence of a recent upper respiratory infection frequently produces CRP in the serum.

3. The results of this survey show that CRP occurs about ten times more often in asthmatic patients with a recent upper respiratory infection than in those without it.

4. In nonallergic children with a recent infection of the upper respiratory tract, the CRP is not present in the blood serum.

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THE DUTCH SOCIETY FOR ALLERGY

The Dutch Society for Allergy has set up an Allergic Drugs Committee. Dr. C. de Lind van Wijngaarden, allergist, is president; Dr. F. A. Nelemans, pharmacologist, is secretary; and Dr. W. F. J. van der Bijl, specialist in internal diseases, is treasurer. The committee will have the cooperation of Mr. H. A. M. van Steenbergen, a pharmaceutical chemist. The purpose of the committee is to study drug intoxications resulting from drugs prescribed by Dutch allergists, to carry on or sponsor clinical research on new drugs or on drugs advocated in the literature, and to publish a list of drugs helpful in the treatment of allergic diseases in addition to those already listed in the Dutch pharmacopoeia. Results of the committee's work will be published in professional journals or in the proceedings of the Dutch Society of Allergy. The address of the Committee is: Cornelis Houtmanstraat 18, Utrecht.

THE GOLD HEADED CANE

WILLIAM MACMICHAEL, M.D.

(Historical Document—Excerpts)

It was in the autumn of 1689. My master*, Dr. Radcliffe, had just then returned from a distant journey in the country, and was much fatigued, when an urgent message reached him at his house in Bow Street, Covent Garden. Snatching me up, he hurried into his carriage, and set off with all speed for Kensington House. . . .

We were ushered through a suite of several rooms, plainly but handsomely furnished by Simon de Brienne; and it seemed to me that the Doctor assumed a more lofty air, and walked with a firmer step, and I was conscious of a gentle pressure of his hand, as he stopped and gazed for a moment on the likeness of the Founder of the College of Physicians, Dr. Linacre, painted by Holbein, which was hanging in one of the rooms, amongst the royal portraits of the Henrys, and several other of the Kings and Queens of England and Scotland.

On entering the sick chamber, which was a small cabinet in the south-east angle of the building, called the Writing Closet, a person of a grave and solemn aspect, apparently about forty years of age, of a thin and weak body, brown hair, and of middle stature, was seen sitting in an armchair, and breathing with great difficulty. The naturally serious character of the King (for it was His Majesty, William the Third) was rendered more melancholy by the distressing symptoms of an asthma, the consequence of the dregs of the smallpox, that had fallen on his lungs. In the absence of the fit, and at other times, his sparkling eyes, large and elevated forehead, and aquiline nose, gave a dignity to his countenance, which, though usually grave and phlegmatic, was said in the day of battle to be susceptible of the most animated expression. "Doctor," said the King, "Bentinck [Earl of Portland] and Zulestein [Earl of Rockford] have been urgent with me that I should again send for you; and though I have great confidence in my two body-physicians here, yet I have heard so much of your great skill, that I desire you will confer with Bidloo and Laurence, whether some other plan might not be adopted. They have plied me so much with aperitives to open my stomach, that I am greatly reduced; my condition is, I think, hazardous, unless you try other measures."

The King seldom spoke so long at a time, his conversation being usually remarkably dry and repulsive; and here His Majesty's speech was inter-

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Reprinted by permission from "The Gold Headed Cane" by William MacMichael, M.D., pages 5-9, Paul B. Hoeber, Inc., New York, 1915. (First edition published in 1827 in England.)

*It is the gold headed cane speaking.

rupted by a deep cough, and he sunk back in his chair exhausted. "May it please Your Majesty," said Dr. Radcliffe, "I must be plain with you, Sir; your case is one of danger, no doubt, but if you will adhere to my prescriptions, I will engage to do you good. The rheum is dripping on your lungs, and will be of fatal consequence to you, unless it be otherwise diverted."—Upon this, Dr. Bidloo, who though expert in the knowledge of some branches of physic, was not always happy or quick in his conjectures, was about to reply. There was something like an insinuation of mala praxis in the last observation; and being somewhat of an irascible temper, the Dutchman, anxious perhaps to return to his duties of professor of anatomy and surgery at Leyden, was indifferent about giving offence to his royal master. But the King, in a calm and sullen manner, imposed silence, and intimated to the physicians to withdraw and consult upon the treatment of his malady. The consultation was short, and the result was, that some medicines should be tried that might have the effect of promoting the flow of saliva. This treatment fully succeeded, for the King was so completely restored that a few months afterwards, he fought the battle of the Boyne.

APPROVED RESIDENCIES AND FELLOWSHIPS IN ALLERGY

The *Journal of the American Medical Association* for September 24, 1955, lists on page 291 the residencies and fellowships in allergy approved by the Council on Medical Education and Hospitals of the American Medical Association, revised to September 1, 1955. The following eighteen hospitals and thirty-two assistant residencies and residencies have been approved for one year of training by the Council and the Subspecialty Board for Allergy of the American Board of Internal Medicine: Army Medical Center Hospital, Washington, D. C. (W. H. Diessner, chief); U. S. Naval Hospital, San Diego, California; Veterans Administration Research Hospital and Northwestern University Medical Center, Chicago, Illinois (S. Feinberg, chief); Veterans Administration Hospital, Pittsburgh, Pennsylvania (L. H. Criep, chief); University of Illinois Research and Educational Hospitals, Chicago, Illinois (Max Samter, chief); Massachusetts General Hospital, Boston, Massachusetts (W. S. Burrage, chief); University Hospital, Ann Arbor, Michigan (J. M. Sheldon, chief); Mayo Foundation, Rochester, Minnesota; Jewish Hospital, Brooklyn, New York (M. Walzer, chief); New York University-Bellevue Medical Center University Hospital, New York City (W. C. Spain, chief); Roosevelt Hospital, New York City (R. A. Cooke, chief); Duke University Hospital, Durham, North Carolina (O. C. E. Hansen-Pruss, chief); Temple University Hospital, Philadelphia, Pennsylvania (Louis Tuft, chief); Montefiore Hospital, Pittsburgh, Pennsylvania (L. H. Criep, chief); University of Virginia Hospital, Charlottesville, Virginia (O. Swineford, chief); and Medical College of Virginia, Hospital Division, Richmond, Virginia (M. E. B. Owens, chief).

Progress in Allergy

HAY FEVER

A Review of the Literature of 1953-1954

MORRIS A. KAPLAN, M.D., F.A.C.A., NORMAN J. EHRLICH, M.D., F.A.C.A., and ABE L. AARONSON, M.D., F.A.C.A.
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FOREWORD

This report is of special interest because a number of chemical, immunologic, and serologic studies are discussed which may offer some possibility of solving the question of the role of the various allergens found in pollens. We know that giant ragweed has at least five different antigens. With the aid of special methods for the preparation of extracts and separation of the antigens, a hope exists that we will have a single, pure substance that can be standardized so that we can begin our scientific studies which will withstand critical analysis. When the individual allergens or fractions found in pollen are completely studied in relationship to their biologic activity as compared to their chemical nature, their true nature can be assayed. New methods for preparation and separation involve nonaqueous solvents, electrophoresis, paper chromatography, and ion-exchange resin fractionation. Homogeneity, purity, and standardization utilize new methods which involve ultra-violet absorption spectra curves and gel diffusion techniques. Serologic studies for antibodies involve special techniques for complement fixation, coated red cells, and inhibition tests. We know that a number of highly purified pollen extracts are still mixtures of antigenic and nonantigenic substances. Naturally, the antibody response to these extracts will be greatly influenced by these mixtures. It is hoped that the newer application of the serologic methods will help clarify our knowledge.

IMMUNOCHEMISTRY

The problem of solving some of the basic fundamental questions of pollen hypersensitivity is much closer to solution due to the excellent studies in the past two years.

Goldfarb et al[88] have prepared and purified a ragweed extract, which is practically colorless, by a new electrophoretic method and by extracting with methanol. By utilizing the absorption spectra, two main absorption bands were reported for the crude aqueous at 2600 Å and 3600 Å. Both of these bands may be correlated to the impurity. The main components separated electrophoretically still showed a band at 2600 Å. When the extracts were leached and laked at 90 per cent methanol extraction, they also showed two bands at 2600 Å and 2600 Å. Biologically, both pigmented and unpigmented preparations are active. Removal of the pigment by electrophoresis leaves an active component colorless at 0.3 u/sec at a pH of 7.4.

Bookman and Wax[24] fractionated an *Ambrosia trifida* solution by passing solutions through columns of various ion-exchange resins. Nitrogenic fractionation occurred which, when tested on known reactors, showed

both active and inactive fractions. There was no correlation between the nitrogen content and the antigenicity of the fractions. This method suggests a new approach to the isolation of the individual components of antigens in pollens.

Pringle,[171] in studying *Ambrosia elatior* pollen proteins, noted only three different free amino groups, and all the protein fractions tested showed similar free amino groups. This suggests the possibility that all ragweed pollen proteins have the same configuration at the free amino positions. Various preparations of *Ambrosia elatior* were arylated with 2,4-dinitrofluorobenzene. In every instance, hydrolysis of these dinitrophenyl proteins yielded 2, 4-dinitroaniline, 2, 4-dinitrophenol, and ε-dinitrophenyllysine.

Criep et al[44] studied the relationship of the pH of allergenic extracts to storage and skin reactivity. Samples of stock allergenic extracts were stored in the refrigerator and tested for change in pH over a six-month period. Those prepared with buffered saline or Coca's solution exhibited the greatest pH stability, while those prepared with sulfoxylate showed a general decrease in pH. No samples were found to change beyond the limits of antigenic activity. Samples of dilute ragweed extract were adjusted in pH to a variety of values, stored at both room and refrigerator temperatures, and observed for pH changes for six months. The effect of temperature changes on the pH was not significant. Change in pH of ragweed extract had little effect on the skin reactivity of either allergic or nonallergic patients.

The utilization of special techniques and methods has helped in examining the active components of pollen extracts. Those individuals who are interested in electrophoresis and ultracentrifugation methods would be wise to read Becker's[13] paper. The usefulness of electrophoresis depends on the fact that many of the molecules of protein and polysaccharide carry electric charges. In ultracentrifugation we take advantage of the fact that all particles have mass and will be affected by centrifugal force. Electrophoresis is defined as migration in solution of charged particles in an electric field. This is the most important work done since Tiselius' work in 1937, using the "Tiselius apparatus." The author describes the apparatus, its method of operation, and the results of study. The first one to build the ultracentrifuge was Svedborg. It is possible for components to have this same mass but different charges, and vice versa. The author gives an excellent basic description of the modus operandi of the Tiselius apparatus and the ultracentrifuge.

Wiedemann[249] reviewed the subject of electrophoresis. Although this is a very complex and technical subject, the methods commonly used are discussed and subjected to critical comparison. For all interested in this subject, the article is highly recommended.

The question as to the nature of allergic antigens is the study of Spies et al [222] who continued their studies on the chemistry of allergens by subjecting one of their fractions CS-13-Endo, a purified fraction of CS-1A, the principal allergen of cottonseed. Trypsin, chymotrypsin, pepsin, and carboxypeptidase were used, and all of these enzymes digested CS-13-Endo. Skin reacting capacity was destroyed by trypsin, but decreased activity remained after chymotrypsin. The authors believe these results show that allergenic activity is caused by protein, and not by unrecognized contaminants in CS-13-Endo. Pepsin and carboxypeptidase digested CS-13-Endo, but to a lesser degree than the other two enzymes. Pepsin and carboxy-

peptidase did not destroy the skin-reacting capacity. The peptic digest of CS-13-Endo was antigenic.

Juhlin-Dannfelt et al[113] report a case of hypersensitiveness to cottonseed in which, on the occasion of the skin examination, the patient went into severe allergic shock. For the next twenty-two days the patient was examined daily in respect to skin titer and sensitiveness to provocation by inhalation of the specific allergen. The examination did not show any definite reduction of the skin titer or the bronchial hypersensitiveness after the shock. During the period of observation the patient was given ACTH during a four-day period, which did not lead to any remarkable changes in the sensitiveness of the patient's skin or bronchial mucous membrane. The case described did not provide any evidence for the occurrence of refractory periods in the hypersensitiveness after an allergic shock.

A number of articles and editorials have been reviewed on the subject of immunology and research in allergy. They are all thought provoking, and show the trend in our thinking. Marrack's[138] "Forty Years of Immunochemistry" is a very comprehensive review. The author is one of the outstanding leaders and contributors to this field, and his personal views and reviews make most interesting and informative reading. Along similar lines but more inclusive are the reflections of Kallos[114] who discusses "Some Immunochemical Aspects of Allergy." This article presents the relationship of anaphylaxis and allergy in review for the past fifty years. We are beginning to realize that we must return to the original contributions to be able to understand how closely all aspects of immunology are related.

An editorial,[61] "Research in Allergy," in *The Journal of Allergy*, January, 1953, mentions simple experimental methods employed in the early days in allergic research, as compared with present immunochemical methods, which are quite complex due to the problem of protein separation. It indicates that fundamental research in allergic diseases is becoming a problem for teams of highly trained workers in basic medical sciences.

Another editorial,[60] "Progress in Allergy—A Plan," in *The Journal of Allergy*, May, 1954, compares individual contributions with collective efforts in the field of allergy. It explains briefly, the newly formed "American Foundation for Allergic Diseases" . . . its needs for funds, etc. It also asks that authors send a copy of their books and reprints to the Foundation's office. Help in the educational program for patients can be met by distributing folders published by the Foundation.

We are still at a loss to explain completely the biochemical mechanism of the allergic reaction. Ungar[242] reports on this subject with a very thought provoking discussion that attempts to define the allergic reaction and to reduce it to its essential constituents. From this he analyzes his thoughts on the biochemical mechanisms. Although not everyone will agree with his concepts, the article is well worth reading.

In an article discussing the role of histamine, Noah et al[156] detected appreciable release of histamine in the blood plasma when whole blood of a clinically sensitive individual was incubated with ragweed antigen. No such increase occurred in unseparated whole blood similarly treated. The discrepancy is believed to be due to the transfer to the plasma of histamine contained in red cells. Greater release of histamine took place in blood samples taken during the ragweed season than in those taken preseasonally.

Dragsted[55] reports on the circulating eosinophil cells in hay fever

patients in relation to specific desensitization. Counting eosinophils one hour after exposure to timothy pollen in hay fever patients, eleven untreated patients and two fungus allergy patients reacted by a rise in the eosinophil count, averaging 46 per cent. Thirteen treated patients showed a fall in eosinophils by 51 per cent.

Best et al[14] report the clinical value of eosinophil counts and the eosinophil response tests. These tests are easy to do and are more accurate than the differential counting of eosinophils on a stained smear of blood. The counting chamber, therefore, replaces the inaccurate differential counting. The normal basal circulating eosinophil count is from 70 to 450 cells per cc of blood. Eosinophilia may be the result of antigen-antibody reactions, humoral factor, bone marrow hyperplasia, or feeding raw liver. Eosinopenia may result from adrenal hyperactivity or other factors. The intravenous Thorn test, using 50 units of ACTH, is of value in determining adrenocortical activity. The eosinophil level of patients receiving corticotropin should be followed by frequent counts at the onset of therapy and periodically thereafter. The diagnostic use of the eosinophilic count is of little value in the diagnosis of adrenal, hypothalamic, or pituitary disease, and should be abandoned until the mechanism of the action of these organs on the eosinophils is clarified.

Dixon[53] discusses "iodination of proteins" method of I^{131} protein measurement and its experimental applications. The antigin I^{131} bovine gamma globulin was prepared in three forms. This procedure is most important in the investigation of the dynamics in the *in vivo* aspects of immune reactions.

Probably some of the most important advances to be reported are those of Wodehouse[254,255] dealing with the use of gel diffusion techniques for identification, analysis, standardization, and therapy with ragweed pollen. Wodehouse found that with these techniques he could reproduce the work of other investigators with greater ease. This would make the precipitin test of Heidelberger, and the reagin neutralization test of McPherson equal to the technique of gel diffusion, which is much easier. Wodehouse utilizes the gel diffusion method of assaying and analyzing antigenic extracts. He uses the law of diffusion, which states that the rate of penetration of a diffusing substance is proportional to some fractional power of its concentration. By this method he presents an *in vitro* system of standardizing allergenic extracts. By means of a carefully selected pollen extract of average potency, the antigen dilution graph may be established for the standard serum, and subsequent extracts may be titrated against it in absentia. By this method Wodehouse studied pollen extracts and found them to be thermolabile. The extracts are destroyed by heat at incubation temperature in the absence of glycerin, with little or no disturbance of the antigen balance.

Augustin[8] isolated and characterized the active components of grass pollen. She found that the active component was a non-dialyzable protein with a molecular weight of 14,000, and was able to develop precipitins for the antigen in rabbits and guinea pigs. Chemically, she was able to crystallize this antigen and separate it electrophoretically. She also used the Oudin gel diffusion technique.

Augustin[9] also in a very comprehensive article discusses standardization of pollen, pointing out the difficulties encountered. Eluting paper chromatograms, she has found pollen to contain peptids, carbohydrates, and combined and uncombined pigments. Ultrafiltration or dialysis remove more

fractions, all inactive by skin tests, while active protein complexes remain. The average molecular weight is 14,000. She found active fractions in three components, which on hydrolysis yield amino acids and carbohydrates. In a discussion of the use of gel diffusion, precipitin tests, and Gradocal membrane, she points out that grasses have antigens in common. In the same paper she reviews the specific blue spot technique in guinea pigs, the methods of Corelti, Boyden, and Coombs, and the gel diffusion technique, pointing out the difficulties of standardization, and concludes that a pure antigen from pollen is the solution.

Bjorklund[17,18] modified his technique for qualitative analysis of gel precipitates with the aid of chemical color reactions. He experimented with three different immunologic systems, showing that the antigens, when combined with antibodies in a gel, retain their affinity for certain dyes. This affords the possibility to study not only the chemical nature of certain antigens but also their immunologic behavior in complex mixtures.

Others have studied the serum of patients suffering from hay fever by the use of special techniques. Britton et al,[28] Gosselin et al,[89] Orlans et al,[160] and Portnoy and Sherman[167,168] each used modifications of serologic techniques involving hemolysis of red cells, complement fixation, agglutination of red cells, and complement inhibition to determine antibodies in ragweed pollen antisera.

Ratner's[180] concept of the physiologic mechanisms of anaphylaxis and allergy is a brief, clear, and concise appraisal of our knowledge of the subject.

Hayes[99] points out that the corticosteroids, particularly cortisone, delay local antibody formation.

Gosselin et al[89] studied serologically grass pollen extracts. Rabbits were inoculated with six different grass extracts, and the sera produced were used in serologic studies of its antigenic nature. Using Boyden's antigen-coated particle technique, they demonstrated the presence of a common antigen in each of the six different pollen extracts. Using an inhibition method, an antigen mosaic characteristic pattern for each of the six different grasses was shown.

FUNGI

Maunsell's[140,141] interest in fungi is demonstrated by her excellent discussion of the subject. She points out the difficulties in culturing airborne molds and in counting mold spores, and advises the use of suction traps in which a known amount of air is drawn into a chamber containing slides or plates. Clouds of fungi can be noted indoors, especially in damp buildings, and dry rot is a hazard in old bombed buildings. Occupations also entail a hazard of sensitization to spores; this is particularly noted among dock workers, secondhand furniture dealers, and gardeners. She noted, too, that there was a tenfold increase in total spore counts inside dwellings where building work was in progress as compared to normal conditions. Symptoms may be due to exposure to high concentrations. In winter the dominant fungus in London is *Penicillium*, and from June to September, *Cladosporium* reaches a very high concentration. Clinically, a fungus allergy may be combined with a pollen allergy during the summer months.

Richards[187] reports on the seasonal periodicity in atmospheric mold spore concentrations through a three-year survey during which he exposed daily culture plates at Cardiff, Wales. Ninety-five per cent of the plates

revealed *Cladosporium, Pullularia, Penicillium, Epicoccum, Phoma, Aspergillus, Botrytis, Oospora, Sporotrichium, Candida,* and *Alternaria* with sterile *Mycelium. Cladosporium,* alone, accounted for 38 per cent. Five molds showed seasonal variation, namely, *Cladosporium, Epicoccus, Alternaria, Botrytis,* and *Pullularia;* less variation was noted among *Aspergillus, Oospora,* and *Candida. Phoma, Penicillium* and *Sporotrichium* were seen all year. *Cladosporium* was noted especially during the warm months, or from June through September.

Richards[188] also studied the indoor dissemination of dry-rot spores, using the gravity slide method, and demonstrated that considerable numbers of dry-rot spores are readily carried by air currents throughout a moderately large house.

Williams[250] reports on investigations carried out in conjunction with the allergy research unit at Cardiff, Wales. A twelve-year study of pollens and molds showed *Cladosporium* to be the most important mold and present in especially high concentrations in late summer.

From South Africa, Ordman[158] reports on allergic conditions in that area, noting particularly that fungus spores contribute to the causation of allergy and that several varieties of fungi have been reported from Johannesburg. He feels that the humidity, vegetation, and high temperatures there contribute to the high incidence of allergy.

Bruskin[36] presents a comprehensive survey of the incidence of fungus spores in the New Brunswick, N. J., area, and a discussion of climatic effects on spore counts. He found that the peak months were June and July, and that the major and most frequently collected organisms were *Hormodendrum, Penicillium, Epicoccum, Alternaria, Pullularia, Aspergillus, Stemphylium, Botrytis, Fusarium, Helminthosporium,* and *Phoma.*

Gregory et al,[92] report on the concentration of basidiospores of dry-rot (Merulius lacrymans) in the air of two affected buildings. They used power-operated suction traps and found 79,500 spores per cubic meter in the cellar, and 16,000 per cubic meter on the first floor. A country house revealed 360,000 per cubic meter in the cellar, as compared to 1,630 on the first floor. An unaffected building revealed less than ten spores per cubic meter.

Hajos and his associates[95] report on the role of *Epidermophyton, Trichophyton,* and *Ochorion* in respiratory allergy in Hungary. They found that *Penicillium, Aspergillus,* and *Mucor* are also causative factors. Specific systematic hyposensitization for a period of six to eight weeks rendered the patient symptom free from thirteen to fourteen months.

From Brunswick, Georgia, Collier and Ferguson[40] report on the incidence and variation with climatic changes. Twenty-eight molds were identified in this area, the dominant molds being *Penicillium, Alternaria, Oospora, Aspergillus,* and *Monilia.* Wind variation at the time of exposure was the most striking of the atmospheric factors on the mold count, although rainfall seemed to clean the air. Seasonal variations were also noted.

Prince and Morrow[170] discuss the relationship of mold fungi selection for therapy. Appropriate diagnostic and therapeutic mold antigens must be selected on the basis of geographic and seasonal incidence, and must be of reliable potency and free from irritants. Appropriately combined mold mixtures representing botanical groups are preferable for treatment.

Everyone is advised to read Schaffer and Seidmon's[202] excellent and comprehensive report. They note that in New Jersey there are three

groups of allergic patients that have mold allergy as an important factor: (1) Group I shows seasonal variations from January to May, from July through mid-August, and from mid-August to the first frost; (2) Group II has perennial symptoms; and (3) Group III has symptoms in damp, humid weather, both summer and winter. An air centrifuge was used twice a week with a fixed amount of air; nevertheless, they note the difficulty in counting and identifying fungi spores. Cultures were serial diluted to obtain slow growers as well as fast growers, and results were tabulated after twenty months. Fifty culturable molds were recovered from the air, with twelve fungi making up 50 per cent of the colonies.

Volterrani[247] reports from Turin, Italy, on the distribution of air-borne mold spores. He found the most common species to be *Cladosporium hebarum, Epicoccum purpurescens, Alternaria tenuis, Thosotorila glutinis, Penicillium expansum, Botrytis cinera, Penicillium digitatum, Cladosporium hebarum var. nigrican, Trichothecium roseum,* and *Mucor mucedo.*

POLLEN

Doyle[54] and Isaac et al[108] in *Public Health Reports* discuss the problem of air pollution and the role of pollen and other noxious substances.

Respiratory symptoms developing from locust sensitivity are reported by Frankland.[76] Of thirty-four laboratory workers who came in contact with the locusts, four developed allergic rhinitis.

Mendes and Cintra[145] report respiratory symptoms from castor bean dust in Bauru, São Paulo. The air pollution was caused by a factory which extracted castor bean oil in this city.

An editorial[59] in *The Journal of the American Medical Association* discusses migration for relief from allergies, and notes that allergies are to be found in each location and that before moving one should know which allergens are to be avoided.

Sands[198] discusses the fact that allergens of dust and pollen are carried great distances, due to the southwest wind, and in a good review on pollinosis Spain[218] discusses the role of weeds in a general public health report.

Speck[221] reports on the atmospheric pollen in the city of Perth, Australia, and environs.

Unger[243] reports on the use of a machine called Pollenex for the removal of pollen. He finds it very efficient in a closed room, removing up to 73 to 75 per cent of the pollens and molds.

The relation of the flowering time of various plants which cause pollen allergy is reported by Virtanan.[246]

Surveys of air-borne pollen and fungus spores constitute tedious and time-consuming effort. Their values can only be appreciated when one realizes that unless the knowledge is available, much useless testing is done. The best treatment of the allergic patient is a specific one, although much therapy is done utilizing the wrong allergens.

Doctors Hyland, Graham, and Steinmetz and Vickers[275] are to be commended for their excellent survey of Maine. Through the combined efforts of the Governor of Maine's Departments of Botany and Entomology, the University of Maine, and the authors, the project was made possible. The results which are published in book form are available to all interested persons. The marked variations from station to station show the effects of wind velocity, wind direction, sunlight, rain, temperature, humidity, and

other barometric factors. Methods, procedures, and evaluation of results are well reported.

As more surveys are done, it becomes increasingly obvious that there are many variations in reported results. Coppelli and Claus[43] report on a comparative survey of anemophilous tree pollen in western Pennsylvania, in which they show that the pollen trees can be divided into two types based on the time of pollination: (1) those that pollinate early, such as the alder, elm, willow, hazelnut, poplar, and maple; and (2) late pollinators, such as the oak, birch, hickory, walnut, ash, beech, hornbeam, and plane trees.

Dingle[52] discusses variations in dispersal of pollens and problems in reporting pollen counts. Wind velocity, speed, direction, stability of air, and local pollen sources are discussed.

Friedewald,[80] reporting on a survey of west Texas, notes that three weeds pollinate in large quantities during September and October in that area: ragweed, careless weed, and tumble weed. Trees of importance are the mountain cedar which pollinates in October and November, Chinese elm in January and September, and mesquite in May. Bermuda grass and Johnson grass pollinate from spring to fall. He also noted that *Alternaria* spores are found during all months except January to May.

Scherr,[203] reporting on ragweed pollination in Charleston, West Virginia, noted that their ragweed season lasted from about August 22 through September 6, with a high point of 150 pollen granules per cubic yard of air.

Kennedy[119] utilized the standard gravity method, and the rotary standard sampler, at ten stations which he selected with regard to variations in vegetation and population density. He felt the rotary standard sampler gave better results, and concluded that there are only two hay fever seasons in the Alberta region: spring hay fever due to trees and shrubs, and summer hay fever due to grasses and weeds. Kessler[121,122] in his report on air-borne pollen and mold spores in Israel suggested that quantity and distribution of the rains were the main factors dominating the picture of pollination. Among the important pollens in that area are pine, grasses, compositae, and amaranth pollen, plus numerous molds.

Williams[250] reports on the pollen surveys carried on for the past twelve years at Cardiff, Wales. Twenty-three pollens were found, of which 60 per cent were grasses. Tree pollens of various kinds were also noted: ash, 7.6 per cent, oak, 5 per cent, elm, 4.1 per cent, and miscellaneous, 3.7 per cent. These were present from February to August.

Smith and Rooks[216] studied the diurnal variations of air-borne ragweed pollen, using a continuous recording volumetric sampler placed in operation during the entire ragweed season. They first determined the efficiency of the sampler in terms of *Ambrosia trifida,* and found that the most critical exposure period was from 9 a.m. to 1 p.m. Only 10 per cent of the pollen was collected from 6 p.m. to 6 a.m.

Wiseman et al[251] studied factors influencing pollen counts on the Ambrose Lightship situated nine miles from the nearest land in New York Harbor, a location free from ragweed plants. They noted that wind direction and velocity were important determinants of the atmospheric concentration of pollen. In 1949 and 1950, only two to three days of westerly winds prevailed, and the seasonal totals at the lightship were 46 to 60 per cent of the New York City totals, suggesting that New York

City receives as much wind-borne ragweed pollen as it raises within its own city borders.

DIAGNOSTIC PROCEDURES

Tuft and Heck[240] studied the literature as well as data gleaned from a questionnaire with these results: Patients do acquire sensitization to new food allergens; skin sensitization changes very little, either as a result of allergen avoidance, or of treatment; skin test reactions may change with advancing age, especially after age fifty, because of a decrease in skin reactivity.

The use of raw and frozen foods as skin-testing materials was reported by Ancona and Schumacher.[4] They found that the allergenic properties of the material were not affected by storage in the frozen state for several months, and that raw foods were innocuous to the skin and non-urticariogenic in allergic and nonallergic patients.

Bloom and his co-authors[21] studied the result of ten foods tested on thirty chosen patients with confirmatory clinical trials, using the intentional feeding method. Skin tests with standard extracts were compared with pepsin and trypsin digests. They suggest that there are changes in the antigenicity of foods due to digestion, but that these occur infrequently, and conclude that foods play a minor role to pollens, inhalants, and infection in cases of allergy.

Fein[66] enumerated and discussed various diagnostic tests available for bacterial, fungus, parasitic, and virus diseases, and those for a group of diseases of unknown etiology. The technique and interpretation of such tests were briefly and concisely stated.

Sheldon and his associates[210] present an interesting survey on skin tests in atopic disease. They point out that the successful management of allergic disease depends on recognizing the causative agent and eliminating it from the patient's environment, or giving him immunologic protection by means of hyposensitization. In general, skin tests are a means of demonstrating the presence of antibodies and a history must always be taken before skin tests are begun. They conclude that the total number of skin tests for an adequate allergic survey is an individualized problem.

The "prick method" of skin testing is described by Harley.[98] It was used by Freeman, and the author believes it to be the best method, requiring a potent extract of the allergen.

An improved allergy testing syringe, consisting of a crown glass barrel, a metal plunger, and a silicone "O" ring as the seal, was described by MacLaren.[135] Axelrad[10] also described a new allergy testing and treatment syringe, using corsol (a new inorganic rubber) together with Cooke's allergy syringe. It has many advantages over the previously used asbestos winding.

Quintero[175] presents an apparatus for washing syringes twenty-one times in three minutes in order to remove foreign proteins from previous usage and thus decrease false reactions. Twenty syringes can be washed at one time by this means.

The use of antihistamines in the diagnosis of respiratory allergy was discussed by Myers.[151] In the author's experience with pediatric allergy, if an antihistamine consistently eliminates or reduces respiratory symptoms, allergic factors are responsible for all or part of the symptoms. He also states that antihistamines are beneficial in diagnosing and treating the cause of nasal obstruction, sneezing, itching, discharge, and cough,

secondary to nasal symptoms. (This paper presents much controversial material.)

Blanton and his associates[20] presented evidence of respiratory allergy in a survey of 37,497 persons. The following statistics were given: Hay fever, 1.5 to 5.3 per cent; perennial hay fever, 0.7 to 2.9 per cent; asthma, 0.5 to 3.3 per cent; and respiratory allergy, 6 per cent. White people were found to be less affected than colored people.

Stevens[224] noted that bacterial infection may cause atopic symptoms in children. Chobot considered this to be an important cause of asthma in 87 per cent of the children he studied. This author found the upper respiratory mucous membranes of the children studied to be hypersensitive to bacterial products in the polyvalent filtrates, and concludes that, as in the skin, the infected areas become sensitized to the nucleoproteins and culture filtrates of these bacteria, so that the nasal mucosa of atopic children with recurrent bacterial rhinitis are sensitized to upper respiratory bacteria.

Asthma may occur with "colds" in children, if they are focally hypersensitive to the bacteria causing the second stage of the "cold," according to Stevens.[223] In the purely infectional type of asthma, attacks occur only with "colds" during winter, not in summer. These patients require bacterial therapy. When a frank or latent bronchiolitis occurs, without bacterial sensitivity, the irritating and inflammatory effects of the infection are sufficient to initiate an attack.

Swineford[230] used pneumococcal polysaccharide, type VI, referred to as a hapten, in further studies in bacterial allergy, as an aerosol spray in guinea pigs sensitized passively with rabbit antiserum. He noted that aerosols of specific haptens elicit respiratory distress of varying intensity. The reactions to inhaled hapten may differ from intravenous hapten, as aerosol desensitization is local and may last as long as nine days.

Dann et al[47] studied the effect of Prantal® given intramuscularly in 25 mg doses in twenty-four patients. They believe, by spirometric study, that this drug has considerable potency as a bronchodilating agent. In the dosage used, this drug was equal in effectiveness to 500 mg of aminophyllin given intravenously, or to 0.25 mg of epinephrine intramuscularly. Side effects were minimal, although some eye and gastrointestinal complaints were noted.

Cohen and Osgood[38] reported on eleven grain workers with respiratory disability, each of whom had worked in an environment of crude grain dust for ten or more years. Changes of chronic bronchitis and recurrent bronchial obstruction with clinical emphysema were frequent. At autopsy, marked pulmonary fibrosis with emphysema was noted. Cor pulmonale was seen in two of these patients.

That odors may give rise to allergic symptoms is the subject of a very interesting article by Brown and Colombo.[30]

Mechaneck[144] described a case of vasomotor rhinitis, together with bronchial asthma, due to locust bean gum dust. The author concludes that gum sensitivity is an occupational hazard.

Ratner and Silbermann[181] presented a critical analysis of the hereditary concept of allergy. They found the incidence of major allergic syndromes in 7 to 10 per cent of the random population. In a group of 3,000 persons, composed of medical students, doctors, and nurses, the general incidence was 10 to 19 per cent. They comment on the discrepancies in published observations as due to the variation in methods of collecting data, the

criteria employed in defining the allergic state, and the extent to which inquiry was made into the individual family incidence of allergy. They conclude that no genetic hypothesis can be made to fit existing data.

An editorial[57] in *The Journal of Allergy* (July, 1953), indicates that published evidence falls short of conclusive proof of the importance of heredity in the etiology of hay fever and asthma groups of allergies. The author suggests studying the descendants of persons having proved allergic diseases, especially in such instances where two known allergic persons marry.

Bowen[27] reported on a survey of fifty-nine sets of twins with allergy in one or both. In fifty-two cases, the clinical allergy was severe enough in only one twin to require medical aid. In only seven cases was there a true bilateral allergy of similar pattern. The author comments that this study is in contradistinction to the concept that allergic manifestations are the result of placental transference. This survey also challenges the concept that, by enforcing maternal dietary restrictions during pregnancy, allergy is less likely to appear in the newborn.

SPECIFIC THERAPY

Rockwell[191] discusses a whole pollen antigen-hydrochloride, which is relatively insoluble and has numerous advantages, namely, retention of potency for longer periods of time, slow absorption, more rapid and larger increase in doses with less danger of generalized reaction. The clinical results of 317 cases treated with this antigen are given.

The prophylaxis of summer hay fever and asthma is discussed by Frankland and Augustin.[77] They found the crude extract to be as effective as the isolated nonprotein component.

A good general discussion of the treatment of ragweed hay fever is presented by Malloy.[138]

Ripps and Fuchs[189] presented a survey of an antigen-antihistamine mixture (ragweed combined with Decapryn Succinate Minergic solution) that was used in treatment of thirty-four highly sensitive hay fever patients. They noted a greater tolerance for this combined mixture, higher ceiling dosages and greater dosage increases being given with safetv. Local and constitutional reactions were infrequent and easily controlled, and more effective clinical relief was obtained.

Sanger and his associates[199] studied the effect of allergen combined with Chlor-Trimeton® administered by injection in desensitization procedures. They found this mixture to be nonirritating, well tolerated, and affording protection against local inflammatory changes.

Thys[238] reports 60 per cent improvement in a series of treated hay fever sufferers, and as high as 75 to 80 per cent in those with less severe pollinosis.

Henderson et al[100] discussed the diagnosis and management of hay fever. They used the term "hav fever" in place of pollinosis, implying the picture of nasal stuffiness, rhinitis, sneezing, lachrymation, itching of the eyes, ears, nose and throat. They estimate that there are 4 million persons in this country who are pollen-sensitive, and that there is no place which is completely pollen-free. This is a good, general discussion of the entire subject of hay fever, with diagnosis, treatment and results well described.

A statistical survey of hay fever in 162 immigrants who came from countries known to be free of ragweed pollens is presented by Shilkret

and Lazarowitz.[211] A control group of 102 American-born persons was used. Onset of symptoms was much later in life in the immigrant group, since they first came in contact with ragweed pollen after they were adults. They also showed a lower incidence of positive familial history of allergy.

Thomas[236] reviewed the ocular manifestations of allergy, some of which may occur concomitantly with hay fever.

Midttun[147] reported a case of anaphylactic death following an injection of dust extract to a patient with chronic bronchial asthma. Only 0.3 ml of 1:10 extract was given, and in two or three minutes there was evidence of sensation in the tongue, followed by cyanotic asphyxia and death.

In 179 cases of respiratory allergy due to inhalants, there was a 9.5 per cent incidence of atopic dermatitis, according to a study made by Diamond.[49] Improvement occurred when therapy with extracts from the antigens involved in the respiratory allergy was started.

Freeman[79] discussed Leonard Noon's ideas about prophylactic inoculations against grass hay fever. As a pioneer, Noon's suggestions are worth consideration. Noon's[157] original article, published in 1911, on the specific treatment against grass hay fever is reprinted in the *International Archives of Allergy and Applied Immunology*.

ANTIHISTAMINES

On the basis of a study of 116 patients using Clistin Maleate®, Johnson[112] found it to be a potent antihistaminic when used in doses of 2 to 4 mg every three to twelve hours. Side effects consisted mainly of sedation, and varied from mild in 9 per cent to moderate and severe in 7 per cent of those individuals studied.

Experiments were carried out by Frankland and Gorrill[78] to determine the efficacy of a new antihistaminic in hay fever and asthma, and also to obtain statistical differences in the incidence of asthma in treated and untreated hay fever patients. They used two antihistamines orally and an inert tablet. Ingenious methods of assessment are described, and each patient was requested to keep a daily record. One hundred-seventy-four patients took part in the trial and numerous tables show the comparative results. The new antihistaminic preparation 405-c-49 compared favorably with Anthisan, although weight for weight it was ten times more potent. It was their feeling that prognosis in hay fever is difficult to determine, but their statistics indicate that the longer hay fever is observed the more likely it is that the patient will develop asthma with it. The presence of asthma makes it less likely that antihistamines will help the hay fever. If specific hyposensitization is given, and this helps the pollen asthma, the remaining hay fever is helped by the antihistamines. Contrary to the observations in the literature on the subject, they felt that there was no evidence in a carefully controlled group that the antihistaminics are of any benefit to the asthma when used as the only form of treatment.

Gruber and Tuft[93] found that 3,4-dihydroxychalcone was not effective in clinical allergy. This flavonoid neither potentiated the effects nor decreased the frequency of side reactions to Pyribenzamine®.

Mothersill et al[148] reported on the chemical and pharmacologic characteristics of Pyronil®, which differs chemically from other available antihistaminic compounds. Pharmacologic observations suggest that it is a potent antihistaminic drug with low toxicity and prolonged action.

Kaplan et al[116] presented their findings on the use of a new antihistaminic compound (FC-1) with a chemical formula unrelated to other histamine antagonists. Seventy per cent of 160 hay fever patients reported good to excellent results with 5 mg administered twice daily. Side effects usually attributable to the antihistaminics were observed in about 15 per cent of these patients.

The sustained release form of Chlor-Trimeton®, known as Teldrin® spansules, was the subject of a report by Green.[91] *In vitro* release data showed that the drug was gradually and continuously released over a period of eight hours, and this was corroborated by *in vivo* studies in dogs. In humans 82 per cent obtained good to excellent results of a symptomatic nature in various allergic syndromes, including hay fever. Side effects were relatively mild.

A series of thirty patients was treated with this same preparation by Rogers.[193] Results in the entire group were good to excellent in twenty-five of these patients, and limited side effects were encountered in three patients. It was his feeling that the preparation produced significantly better results than those obtained with the same drug in tablet form.

Teldrin® spansules was again the subject of a paper by Mulligan[149] who used them in 128 patients, mostly those with hay fever. Chlor-Trimeton® in various forms was used, and patient preference was expressed for the spansules. Drowsiness was the primary side effect, but longer action eliminated the need for frequent dosage.

Naranjo and de Naranjo[153] reported on a rather complete study of the possible synergistic action of the combined use of antihistaminics. They found that a combination of Neo-antergan®, Neohetramine® and Trimeton® exhibited a supra-additive synergism in counteracting experimental histamine asthma, and, to a somewhat lesser degree, other histamine actions. There appeared to be a lack of supra-additive toxicity. These same authors' experiments showed that in guinea pigs all seven antihistaminics used were inactivated in a large proportion in the liver.

With the antihistaminic Bristamin®, Seyler and Simon[209] obtained excellent results in 31 per cent of their cases, good results in 51 per cent, and poor results in 18 per cent. Side reactions occurred in 6.5 per cent and were severe enough to necessitate discontinuance in two patients. They felt that Bristamin® in 50 mg dosage was a very definite addition to the available antihistaminic drugs.

A report[220] of the committee on new drugs of the American Academy of Allergy on compound 4445 (Pfizer) showed it to be only a fairly active antihistamine, but the low incidence of side effects makes it desirable for patients who cannot tolerate the more potent preparations. Like other such drugs, its chief value is the relief of rhinorrhea and sneezing; it was ineffectual in asthma.

Swartz[227] felt that diphenylpyraline was an effective antihistamine drug for uncomplicated hay fever. He used an average dosage of 2 to 4 mg three times a day, with minor side effects of no great inconvenience.

von Bigliardi[248] investigated a new antihistaminic, Sandosten AS716 (Sandoz), reporting good results, especially a reduction in vascular permeability and a synergistic action when used with calcium.

Jenkins[110] felt that the use of Chlor-Trimeton® Injectable permits the subcutaneous and intravenous administration of a low dosage, low volume, effective antihistaminic agent without discomfort to the patient. In hyposensitization therapy this solution, combined with a specific antigen

extract, permitted the administration of much larger dosage of this extract in sensitive individuals. The incidence of side effects was low, and disappeared on discontinuance. He felt that this combination made possible a more adequately functioning hyposensitization program for those individuals who formerly exhibited severe reaction on minimal exposure to the offending agent.

Spearman,[219] using this preparation on a group of 488 patients with various allergies combined with treatment antigens, considered that the results were extremely beneficial in that both local and systemic reactions were lessened. The dosage of the antigens could be considerably increased, and the patients were usually given immediate temporary improvement of their symptoms. He considered that this combination of treatment was so useful that in the future it may become a part of standard treatment practice.

Taub et al[232] also reported on their experiences with this preparation in specific allergy therapy, and were of the opinion that it effectively prevented severe reactions.

An excellent and interesting historical discussion of histamine and antihistaminics is presented by Halpern.[96]

Gill-Carey[87] reported an instance of a child, sixteen months of age, who took eighteen tablets of Perazil® (900 mg) and soon afterwards had generalized convulsions which continued for seven hours. Treatment with anticonvulsant drugs and atropine were used.

Twenty-three cases of altered personality in children, due ostensibly to certain antihistaminics, were reported by Schaffer.[201] With cessation of the offending antihistaminic drug, there was a complete reversal to the normal state in two to three days.

Macaulay[134] observed, during the course of investigation and treatment of 3,000 cases of allergic rhinitis, that in nine cases antihistamine therapy produced relief of the symptoms treated, but coincidentally asthma appeared. In most cases this effect was reversible with cessation of therapy.

Wortman[259] prescribed Plimasin® (Pyribenzamine® and Ritalin®) which is a central nervous system stimulant, to twenty-three patients with hay fever. Results were satisfactory, with rare and only mild side effects. Hoechli and Wolfer-Bianchi[104] treated thirty-six hay fever patients with the same preparation, claiming good to very good results in thirty-one cases. Findeisin[71] carried out trials with Plimasin® in 310 cases of pollen allergy, which seemed to indicate that this preparation combined excellent antiallergic properties with low toxicity.

The use of large doses of antihistamine in severe allergic crises was advised by Antos.[5]

USES AND DANGERS OF STEROIDS

Steroid therapy in allergic disorders continues to hold the limelight in the literature, as it has for the past several years. More definite now are the indications for the use of cortisone, ACTH, and their allied preparations, but always are the abuses and dangers set forth by the many investigators.

Brown and Seideman[32] studied forty patients with ragweed pollinosis who had obtained poor results from hyposensitization therapy or who had received no previous treatment from August 15 to September 30, 1952. Twenty males and an equal number of females were used. Each received five- to eight-day courses of 5 and 10 mg doses of cortisone

acetate, orally, in combination with 25 to 50 mg doses of an antihistamine. The results from each course of treatment were evaluated by co-variance analysis; the ratings of symptom intensity were adjusted, so that these results represent data obtained from patients exposed to a uniform pollen concentration. Statistically, no significant difference was noted in the results of treatment with the various dosage and drug combinations used, but the correlation between records of symptom intensity and pollen count was noteworthy. The metabolism was not affected adversely by the small doses of cortisone used.

Stewart and Kawa[225,226] used ACTH, cortisone, and a combination of both on thirty-three patients with allergic rhinitis. Six months after treatment, nineteen patients were free from symptoms, ten were much improved, and two were improved. The authors found that after suspension of treatment, symptoms gradually disappeared. (This is not the usual result reported by most investigators.)

Irwin and his co-workers[106,107] reported on the maintenance dosage of cortisone in intractable asthma. They report on six patients with perennial asthma, in whom the usual forms of therapy had failed, but who had been helped by cortisone. They suggest the "trial and error" method to determine the smallest possible maintenance dose, and indicate that even very small doses represent hyperadrenocorticism and are capable of producing Cushing's syndrome with osteoporosis.

Evans[64] reports on the use of cortogen acetate with Chlor-Trimeton® maleate therapy in allergy rhinitis, using topical application. The author studied patients with grass pollen sensitivity, ragweed pollen allergy, or a combination of both. He concludes that very few side reactions occurred, and that Cortogen®-Chlor-Trimeton® solution is a valuable adjunct in therapy.

A report on the present knowledge of hydrocortisone, its relation to sensitization phenomena, as well as its therapeutic use in the field of allergy is presented by Di Nardo.[51] He also reports the result of therapy in sixteen cases of bronchial asthma.

Pennypacker[165] reports on hydrocortisone alcohol in the local treatment of hay fever, in the form of Vasocort,® which combines a very dilute (0.20 per cent) solution of hydrocortisone alcohol with two vasoconstrictors. The author concludes that this preparation seems to exert an ameliorating action on allergic nasal tissue.

In an editorial[62] in *The Journal of Allergy*, the editor asks, "Should one use ACTH and adrenal corticosteroids in seasonal allergies?" The editor answers "yes" to his query, if all cautions as to dosage and the patient's general reactions are most carefully observed.

Bloom and Markow[20] present an evaluation of a natural steroid complex (Marisone®) in the treatment of allergic disorders. In all, eighty-one patients were treated, thirty-six of whom were hay fever sufferers. Of this group, 41 per cent yielded satisfactory results, especially for relief of nasal blocking, but relief was not persistent in spite of continued medication. Twenty-seven per cent of the patients showed some side reactions.

Six patients with pollinosis, and seven others with asthma, were studied by Robecchi and Cartesegna,[190] using an aerosol composed of hydrocortisone acetate in isotonic saline. Relief occurred in four of six patients with pollinosis, and only one of seven with asthma reported no relief.

Fifty-one patients with hay fever, ten of whom also had seasonal asthma, and all of whom had failed to benefit from specific pollen-plus-antihista-

minic therapy were studied by Schiller and Lowell.[204,205] All received one or more four-day courses of oral cortisone, and only nine patients failed to respond on the dosage used (100 mg daily).

Schwartz[207] reports on a study of thirty-nine patients with bronchial asthma and ten with ragweed hay fever, all of whom received oral hydrocortisone tablets, with excellent relief in twenty of the asthmatic patients and in seven hay fever victims. Where cortisone had been previously used, the drug studied was as effective in fifteen patients, and superior in eight. Side effects were observed in two patients, requiring discontinuance of the hydrocortisone.

Traynor et al[239] used hydrocortisone in the treatment of pollinosis and felt that its use was justified in carefully selected cases, and that, if used judiciously, it can be expected to produce benefit with minimal risk of untoward reactions.

The use of cortisone and hydrocortisone for prolonged therapy was reported by Arbesman and Richard.[6] They used cortisone in 300 mg dosage the first day, 200 mg the second day, and then 100 mg daily for four to five days, after which the dose was gradually reduced to a maintenance level. Hydrocortisone was administered as follows: 240 mg the first day; 160 mg the second day; then 80 mg daily until a maintenance level was reached. Both drugs were used for prolonged therapy, and the hydrocortisone was at least as effective in the relief of asthma. The comparable effective dose of hydrocortisone was approximately two-thirds that of cortisone.

Lovell and his co-workers[133] report data on nineteen patients with severe bronchial asthma, who received cortisone for a year or more. Seventeen maintained a satisfactory state of health, although no evidence was obtained that the underlying pulmonary disease had been materially influenced by treatment. Two of the patients, who had improved initially, gradually became worse despite therapy and were considered failures. The chief side effects were weight gain and hypertension.

Gelfand[86] studied eighteen cases of bronchial asthma and nine cases of allergic dermatitis who were treated with cortisone, or ACTH, or both. The etiologic factors were inhalants, contactants, ingestants, and infection. Excellent results occurred in all but three of the eighteen asthmatic patients, and in all nine of the patients with allergic dermatitis. There was only one true failure. The author concludes that the steroid hormones, when properly used, constitute one of the most important additions to the allergist's armamentarium.

Jean et al[109] report on the use of adrencorticotropic hormone in gelatin (Armour's ACTHAR Gel®) on twenty ragweed sensitive patients. This procedure proved to be an effective form of symptomatic therapy, and the side effects were temporary, disappearing when therapy was discontinued. Their indications for using corticotropic gel were: (1) Patients who come in too late for specific therapy; (2) patients who do not tolerate pollen therapy; and (3) patients who do not respond to the usual treatment with pollen extract.

ACTH in gelatin was used by Levin[130] on twenty-six adults and eleven children with various acute allergic states, and good to excellent results were observed in all cases. This method allows ambulatory therapy in patients who would otherwise require hospitalization, but the need for concomitant symptomatic treatment was stressed. The use of ACTH gel did not obviate the need for careful and thorough allergic study and treatment.

McGehee and MacLean[143] reported on their experiences with ACTH and cortisone over a period of two and one-half years at Guy's Hospital, London. Disease processes were usually controlled in seven to fourteen days. Of the 185 patients studied, there were three cases of gastrointestinal perforation, with two deaths. Acute psychosis occurred in three patients and steroid diabetes in one. In the majority of their patients, the results were satisfactory. In psoriasis, the result was poor.

Clinical studies on a new long-acting adrencorticotropic pituitary hormone containing zinc were reported by Bonner and Homberger.[25] Their preparation consisted of zinc hydroxide combined with corticotropin in a simple aqueous vehicle which they discovered was stable and easy to inject. Their investigations were made to determine the degree of activity, duration of action, comparison with ACTH-gelatin preparation, and comparison of its effects with those of other long-lasting ACTH preparations. The authors conclude that their material permits a reduction in dosage, in the number of injections necessary for equal effects, and that it is easier to handle than gelatin suspensions.

Seidmon and Schaffer[208] reported on Cortogen®-Chlor-Trimeton® nasal suspensions used in treatment of allergic rhinitis. They feel it is a safe preparation for intranasal usage and is equally well tolerated by adults and children, with only transitory and mild local reactions.

The effect of cortisone acetate and hydrocortisone acetate administration in clinically therapeutic doses on the development of circulating agglutinins in human beings, both during the initial immunization and anamnestically, was studied by Friedman.[81] Six patients received cortisone or hydrocortisone for the first week, after injection of 0.5 ml of typhoid vaccine. Controls received the vaccine only. Three weeks after the first injection of the vaccine, it was reinjected and the treated patients again received hormone for seven days. All patients were followed for an additional two weeks. Antityphoid H and O agglutinin titers were obtained at the beginning and weekly thereafter for six weeks. Marked variability occurred in the H and O titers. Adrenal cortical hormones did not appear to influence the antityphoid agglutinin titers in man. The capacity of humans to produce antibodies varies markedly. The author feels that the results are inconclusive and at variance with animal experimentation.

Irwin and Burrage[106] reviewed experimental and clinical experiences with cortisone and corticotropin in allergic diseases. There were no changes in the size of reactions when blood for passive transfer was taken prior to or after administration of corticotropin. Studies were made on the blood vessels of the bulbar conjunctiva by means of a stereoscopic microscope, using asthmatic patients during and after cortisone therapy. They found that the arteries became constricted and the venules dilated, and that the red cells formed aggregates which were more predominant on the venous side.

In an editorial[58] appearing in the March, 1954, *Journal of Allergy*, the editor urges thorough familiarity with side effects and alertness to their occurrence in using cortisone and corticotropin. He states that the therapeutic effect of these hormones is probably due to the creation of a state of hyperadrenalism, and that the mental effects may be quite serious. The activation of latent tuberculosis or peptic ulcer must be remembered. Decalcification of the skeleton may occur and partial atrophy of the adrenal cortex can take place. He concludes that recognition of the above facts makes it obvious that prolonged treatment with cortisone must not be taken lightly.

Sauer[200] and his colleagues reported on ten patients in whom serious gastrointestinal manifestations appeared during or after administration of cortisone or corticotropin. Death occurred in one patient with chronic ulcerative colitis, in whom perforation of the cecum with peritonitis developed. Perforation of the bowel with peritonitis occurred in two of four patients with regional enteritis. One patient with peptic ulcer suffered a massive hemorrhage and ultimately died of adrenal insufficiency after surgical removal of the ulcer. Ulcerative rectal lesions developed in three patients. The authors urge caution in the use of these hormones.

Two more deaths following ACTH and cortisone therapy were reported by Wold.[256] The first was due to lysis of an old tuberculous lesion, resulting in fatal miliary tuberculosis, tuberculous meningitis, and a tuberculous basilar abscess. The second patient, as a result of prolonged cortisone therapy, died in cardiac arrest while undergoing anesthesia for repair of a hip fracture.

Peabody et al[167] report on the Hamman-Rich syndrome (acute diffuse interstitial fibrosis of the lung) in three patients. The duration was five and one-half months to nine years, and all three were given ACTH or cortisone. In one, who was acutely ill, there was roentgenologic evidence of clearing of the pulmonary tissue with symptomatic improvement, but as the drugs were gradually withdrawn, there was an exacerbation of dyspnea and cyanosis, and despite large doses of both hormones the patient died within twenty-four hours. The second patient used cortisone for three weeks, during which time there was no evidence of improvement. Death was due to respiratory insufficiency. The third patient was treated with ACTH for twenty-seven days and became dyspneic when the dose was reduced. Large amounts of ACTH and cortisone did not prevent death from respiratory failure.

Forgacs and his colleagues[74] report a case of a fifty-three-year-old woman suffering from primary chronic polyarthritis, who received a ten-day course of therapy with ACTH. On the eleventh day she suddenly had an urticarial eruption which disappeared after interruption of treatment. Skin tests with pig liver, pig-meat extracts, and peptone were negative, while tests with ACTH were positive. Tests with dry powder from bovine hypophysis were positive, but were negative with other hypophyseal preparations. Prausnitz-Küstner reaction was positive with all three ACTH preparations used. The authors conclude that this is a genuine ACTH allergy.

An anaphylactoid reaction due to ACTH derived from beef and pork, with positive Prausnitz-Küstner reaction, is reported by Swift.[228]

A forty-five-year-old female with bronchial asthma was treated orally with 25 mg of cortisone daily by Komar and Koch.[125] On the fifth day she suddenly developed chills and fever, and pneumonia was diagnosed. 400,000 units of penicillin in beeswax and oil was injected, following which she felt unwell, was itchy, and had edema of the eyelids. She improved on calcium, Benadryl,® and asthmolysin. The following day, 100,000 units of crystalline penicillin was injected (since the authors were suspicious of the beeswax oil), and the patient became severely dyspneic and had edema of the face. She died ten minutes later. Autopsy revealed edema and inflammation of the lungs, subendocardial bleeding, and adrenal atrophy.

Rappaport et al[178] studied the mucoproteins of the nasal mucosa in patients who were ragweed-sensitive before and after treatment with corticotropin. Biopsy studies of the nasal mucosa showed changes in the connective tissue matrix and connective tissue cells in allergy, and the extent

of these changes was related to the severity and duration of exposure. Untreated allergic patients showed a decrease in glycoprotein staining of connective tissue cells, of ground substance, and of the basement membranes of the surface epithelium, capillaries, and glands. Interepithelial cement of surface and gland cells was diminished and mucigen granules of the glands were decreased. Corticotropin reversed these changes.

Bormioli[26] calls attention to the fleeting nature of the results obtained in allergic rhinitis by application of cortisone in the nasal mucosa by means of aerosol or spray, and to the untoward effects which may be associated with the parenteral route. He discusses the histopathology with microphotograms, showing changes brought about by injection of cortisone into the nasal mucosa in acute allergic phenomena. He concludes that this method is the most rational and fastest for interruption of an allergic-hyperergic explosion.

Rajka and Vincze[177] discuss the development of allergic reaction even in office workers who are in contact with the production of a new antihistamine preparation, Ahistan. Skin inflammation was produced primarily by an intermediate product, through contact and inhalation. Ahistan, the end product, is only minutely responsible for the skin eruption. Skin inflammations were also noted during the production of Isonicide. In two cases, epicutaneous and scarification tests were positive with both raw and purified preparations. Skin inflammations in workers with Threomycin (Chloramphenicol) production is due to strong irritating action of Bromacetophenon. Three positive reactors to the latter were found.

NON-SPECIFIC THERAPY

The specific treatment of hay fever still remains the best hope for good relief. The antihistaminics are a definite help in the control of symptoms and the corticosteroids still have to prove their value, although for the acute symptoms they are worthy of trial. Other methods are still being used and several drugs are useful for some of the symptoms associated with pollinosis.

Ruhnke[196] reports on the use of homologous dry serum in pollen therapy, with some results. This was a hopeful idea of years ago.

Sicuteri and Monfardini[213] report on the use of histamine and Neo-Antergan® in the treatment of allergic disorders with some suggestion of improvement.

Hay fever was treated with histamine with a good measure of success by Lapteva.[126] This has been reported before with results which were equivocal. In our hands, it has been unsuccessful.

Fenton[70] uses Piromen® as an adjunct in hay fever cases not successfully responding to conventional therapy. In the hands of many, including ourselves, results have not been so fortunate. Piromen® has been used with fair success by Aronoff and Ghaemi.[7]

Dees et al[50] report excellent results in children having asthmatic symptoms, with "Nephenalin Pediatric," a tablet containing N-isopropylarterenol in a red outer-coating, 5 mg, theophylline, 100 mg, ephedrine sulphate, 12 mg, and phenobarbital, 8 mg, in an inner nucleus. Others have used compounds containing one or more of these ingredients with some results.

Brugel and Hennex[35] used Visammin with improvement in similar patients as did Mulligan[150] and Tuft.[241]

For sublingual administration Brown[35] used a preparation containing

10 mg isopropylarterenol and 100 mg benzyl-nicotinamide with good results. Baker[11] did a similar study with good results.

Bickerman and Beck[15] evaluated four bronchodilator agents and found that Cardalin, Nephenalin,® and Dainite® (NR) were good. Toryn® was reported to be an excellent synthetic cough depressant by Abelmann et al.[1]

Unger[245] points out that hay fever patients may have an associated infectious component which is best treated with an autogenous vaccine.

Kaplan et al[115] studied the effect of Biomydrin,® a nasal solution containing decongestant, mucolytic, antibiotic, and antihistaminic agents, during a ragweed pollinating season. They did not note any change in bacterial or cytologic status through the use of this solution under the conditions of the experiment, but all patients agreed that they were symptomatically improved. No evidence of sensitization to ingredients was noted nor were any habituation, addiction, or significant side effects encountered.

MISCELLANEOUS

Ouer[161] studied solutions of algin and epinephrine and found it is possible to control the viscosity, as well as absorption, assimilation, and action of these mixtures, by varying the concentration of algin. Prolongation of therapeutic response had been demonstrated and he felt that these solutions are effective aids in allergic disorders.

Naterman[154] prepared a suspension of epinephrine base in Thioglycolate acid, with glycerin and phenol, and another solution of sodium hydroxide and glycerin. It was his feeling that proper mixtures of this suspension gave therapeutic results as prompt as solutions of epinephrine, and as prolonged as suspension of epinephrine in oil.

Thirty-four allergic patients were given six to eight tablets daily of a combination of tyrosine, niacin, and pyridoxine by MacLaren et al,[137] and it was their impression that this mixture did not favorably influence these cases of allergy. Connor[42] used this same combination in patients with various allergic syndromes and concluded that it was completely non-toxic, particularly effective in pediatric practice, and improved a high percentage of his cases, and therefore was a valuable aid in the treatment of allergies. Two such diametrically opposed viewpoints are extremely difficult to reconcile.

Frank and MacLaren[75] administered a new anticholinergic drug, Prantal® methylsulphate, orally to patients with various allergies, nine of whom had nasal allergy. The drug orally did not satisfactorily relieve asthmatic symptoms, but showed a relatively high degree of symptomatic relief from sneezing and rhinorrhea. Certainly more investigation is warranted in view of the paucity of clinical material presented.

Woodrow[258] attributes dramatic relief of hay fever symptoms to a combination of amphetamine and amobarbital.

Eight uncomplicated seasonal hay fever patients were treated with Biomydrin® spray by Wittich,[252] and he reports that seven obtained excellent relief. It is somewhat difficult to analyze this report as it appears that these patients continued on other forms of therapy as well, and any "increased beneficial" effects of the spray carefully noted. Obviously, at best, this is a difficult task.

Fenton[70] used Piromen® as an adjunct therapy in sixty-three cases of allergic diseases unresponsive to previous conventional therapy. He observed beneficial results in 73 per cent of these cases. Although protocol details were omitted, it was his feeling that Piromen appears to increase

the efficacy of concomitant therapeutic measures. MacLaren and Frank[136] used this preparation in various allergies, and it was their impression that their study did not reveal any obvious specific effect by Piromen® on allergic disease. This preparation was used by Fond[72] on thirty-five patients with asthma, and it was his feeling that it was of doubtful value.

Fabricant[65] stresses the importance of physiological pH in nasal solutions.

Parish[162] reported on the use of a new sympathomimetic compound, Tyzine,® in an aqueous solution as a nasal decongestant. A large majority of his patients appeared to obtain excellent results. The vasoconstrictive action lasted from three to four hours after instillation. No unpleasant side effects were noted.

A report appeared by Felder[69] on the use of the patient's own blood with sodium citrate in the treatment of hay fever.

Several reviews appeared, one by Silbert[214] with a general discussion of the etiology and treatment of nasal allergy. Another review of a fine program of the British Association of Allergists,[184] appeared in the *International Archives of Allergy and Applied Immunology*. Thomas[235] presented a historical review of the development of the field of allergy since the turn of the century.

Rappaport,[179] in the President's address to the American Academy of Allergy, stressed the importance of the American Foundation for Allergic Diseases in the fostering of future research and education in the field of allergy. Peshkin,[166] in a similar address to The American College of Allergists, discussed the Foundation and, in general, the development of allergy.

Rackemann[176] discussed the long-range care of allergic children in the *Medical Clinics of North America*, and an entire issue of the *Practitioner*[234A] was devoted to the subject of allergy.

Kaplan, Ehrlich, and Aaronson[117,118] presented a comprehensive review of the literature in reference to hay fever, and Collins-Williams and Ratner[41] continued their critical review of the literature on pediatric allergy started last year.

A general review of pollinosis and the role of weeds appeared by Spain,[218] in the *Public Health Reports*.

A timely and important report by Abramson[2] revealed that twenty-nine cases of poliomyelitis were reported by allergists during a nation-wide survey of 153,749 patients receiving preseasonal and seasonal pollen therapy. This is approximately the anticipated rate. Immunization by pollen extracts does not increase the incidence of infantile paralysis, nor does this type of immunization increase bulbar paralysis or affect the location of paralysis when it occurs.

Fromer and Burrage[83] presented cases of ragweed oil dermatitis, and recommend as treatment avoidance of exposure and specific desensitization. It was their feeling that the injection form of desensitization gave results comparable to that seen in hay fever hyposensitization.

An editorial calling attention to the increasing number of acute reactions to penicillin[56] is included to alert attention to the fact that many unpleasant experiences can be avoided by taking a complete allergic history and utilizing the scratch test to prevent severe immediate anaphylactoid reactions, including fatal anaphylaxis. Among those reporting severe constitutional reactions, including fatal anaphylaxis, are Sohval,[217] Nikishen,[155] Mayer et al,[142] Curphey,[46] Larsen,[128] Kern and Wimberly,[120] Gutmann,[94] and Fein-

berg et al.[68] Several of these authors suggest the use of the skin test which we have found invaluable in avoiding fatal anaphylaxis.

The injudicious use of Fowler's solutions is again called to attention only to condemn it because of the toxic reactions following its use. Those reporting toxicity from arsenic are Blumenthal,[22] Gattner,[85] and Milikan.[169]

Criep and Ribeiro[45] report three fatalities from procaine HCl, in which death followed an immediate anaphylactic reaction. We again suggest skin testing to modify the severe allergic responses resulting from injection of the drug.

BOOK REVIEWS

A large number of books have appeared in the past two years dealing with all phases of allergy. Although many of these books only touch lightly on some particular phase of pollinosis, all are included in this review so that the allergist may have a source of reference.

On the subject of immunochemistry, Gadlowski[272] presents an original concept in his "Enzymatic Concept of Anaphylaxis and Allergy." Raffel's "Immunity, Hypersensitivity, Serology"[281] is an excellent text dealing with the available facts in concise form, and is very useful as a textbook.

The nature and significance of the antibody response was the subject of a symposium held under the auspices of the New York Academy of Medicine, and later edited by A. M. Pappenheimer, Jr.[279] and published. It is an excellent reference book for the worker active in immunology.

Three excellent textbooks on allergy, each with special features, were published during this period. Hansel[273] and Vaughan[290] are very thorough in their coverage of the subject. Black's revision of Vaughan's "Practice of Allergy" is now in its third revision. A companion book, "Primer of Allergy" by Vaughan,[291] has also been completely rewritten by Black. It is intended for the medical student and lay person interested in allergy. The EENT sections in Hansel's "Clinical Allergy" are the best on the subject.

Sheldon, Lovell, and Mathew's "Manual of Clinical Allergy"[286] is an outgrowth of their lectures to medical students. Much of the book is devoted to descriptions of laboratory procedures, and it is therefore excellent for teaching purposes.

A number of books appeared written especially for lay persons and allergic individuals, including those of Swartz, Sammis, Feinberg, and Berglund and Nichols. Swartz's "The Allergic Child"[287] is devoted solely to the layman and is intended to show the parents how to recognize various allergic conditions and impress upon them the necessity of early and prompt treatment. Sammis's[282] book, which deals with the allergic patient, his world, and the sources of allergens, is designed to enable the allergic patient to co-operate intelligently with his physician.

Feinberg's[269] four pamphlets—"Breathe Easy," "One Man's Food" "Skin Deep," and "Allergy is Everybody's Business"—explain in simple lay language the intricacies, complexities, and complications which befall the allergic individual. Prepared for the Blue Cross Commission as its contribution toward better understanding by the public of the several forms of allergy, they are actually part of an educational program.

Berglund and Nichols[262] dedicate their volume, "It's Not All in Your Mind," "to those who suffer and die needlessly because of ignorance and false information" because their allergic diseases are falsely attributed to psychosomatic causes. This might be called a rebuttal to the psychoanalysts and psychosomaticists who have written extensively on their side of the

subject. The immunologic concept of allergy as incorporated into this book adds no strength to the authors' efforts.

Bucher's "Nutrition and Diet in Allergy"[263] is written for the allergic person. It is useful to dietitians and members of the medical profession, and is a good reference for sources of foods.

A group of books which deal with therapeutic advances in allergy, progress reports, and special views of authors are the sections on allergy in Conn's "Current Therapy, 1953"[266] and 1954,[267] Fishbein's "Medical Progress, 1953"[270] and 1954,[271] and Beckman's "Yearbook of Drug Therapy,"[260,261] 1953-1954 and 1954-1955 series.

A number of books in foreign languages have appeared to swell our ever-growing library of books dealing with allergy. Vallery-Radot's "L'-Asthma de l'Adulte"[289] discusses the treatment of asthma in the adult. This book is very popular in France. Colleson and Pierson[265] discuss allergy and the nervous system in "Les Allergies et le Systeme Nerveux." Hugo Kammerer's "Allergische Krankheiten"[277] is a section of the Handbook of Internal Medicine. It is a very comprehensive discussion of allergic diseases. Klewitz[278] presents an excellent book discussing asthma and pollen allergy.

Other books well worth reading are: Segal's "Chronic Pulmonary Emphysema,"[285] Coca's "Familial Non-Reaginic Food Allergy,"[264] Waldbott's "Contact Dermatitis,"[292] and Hepler's "Manual of Clinical Laboratory Methods."[274]

A new foreign journal in allergy, *Folia Allergologica*, the official organ of the Italian Society of Allergology, appeared this year. It will be published bi-monthly and will contain original articles and reviews of world allergology.

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NEWS OF COLLEGE MEMBERS

Dr. Mayer A. Green, Pittsburgh, Pennsylvania, presented a paper entitled "Allergy in General Practice" on September 23, 1955, at the annual convention of the Pennsylvania Medical Society held in Pittsburgh, Pennsylvania.

By Law Amendments

At its last meeting held in the Walnut Room of the Morrison Hotel in Chicago, Illinois, on Saturday, April 30, 1955, after Dr. Wittich had announced his intention to make this his final year in office, the Board of Regents decided that the duties and responsibilities of the combined office of "Secretary-Treasurer" have grown too heavy for any one person to longer assume and carry on alone, and that, effective as of the annual election in 1956, the joint office of "Secretary-Treasurer" be abolished and two separate offices created in lieu thereof (one that of "Secretary" and the other that of "Treasurer") and that they shall not be simultaneously held by the same person.

While this subject was under discussion and consideration by the Board, and before an appropriate resolution was actually adopted authorizing necessary By Law amendments to effectuate such a change, Counsel called attention to the fact that such a resolution, when passed, must make provision for redefining the duties and responsibilities of the old office of "Secretary-Treasurer" and apportioning the same between the two newly created offices of "Secretary" and "Treasurer." It must also authorize corrections and changes which may now have to be made in any other By Law passages affected by this amendment in order to eliminate any inconsistencies resulting therefrom. Counsel also said that when the time comes for making its selections for the official slate which will be voted upon at the annual election in 1956, the Nominating Committee must name one candidate for the new office of "Secretary" and one candidate for the new office of "Treasurer."

The resolution, as it was finally adopted by the Board amending the By Law in question, made the amendment effective as of the annual meeting in 1956. It also contained a provision that Counsel re-examine our By Laws and make certain that any inconsistencies caused thereby are eliminated by redrafting all such By Law provisions so affected, and that they are thereafter to be published in the ANNALS at least 30 days prior to the date when the new By Law amendments or changes take effect, thus giving all members full opportunity to see and read these provisions in print and familiarize themselves therewith before they actually become effective.

The work of drafting these By Law amendments, and correcting or redrafting other By Law provisions affected thereby, has now been completed in accordance with the resolution so adopted by the Board of Regents, and these amendments, changes, and corrections as they are herein published will become effective when our next annual meeting is held in April, 1956.

In order to further facilitate and make more readily understandable these several amendments and changes, they are herein set forth in italics. Also published at this time are other By Law amendments adopted and made effective since our By Laws were last printed in booklet form in 1953.—E.B.

ARTICLE V. BOARD OF REGENTS

Section 7. Officers

(a) Number, election and appointment.—The officers of the College shall consist of a President, a President-Elect, a First Vice President, a Second Vice President, an Executive Vice President, *a Secretary, a Treasurer,* a Counsel, and such other or additional officers as the Board of Regents may from time to time designate and

fix. The offices of Executive Vice President and of Counsel shall not be elective but appointive offices to be filled by the Board of Regents. *The same individual may hold both offices.* All other officers shall be elected by the Fellows of the College at their annual meetings. If in any given year no annual meeting is held, the Board of Regents shall arrange for the election of new officers by mail vote. All officers shall assume their offices immediately following their election and they shall serve for a term of one year or until their respective successors are elected and qualify. *No two elective offices shall be held by the same person.*

(b) The President—(no change)
(c) The President-Elect—(no change)
(d) The Vice Presidents—(no change)

(e) The Executive Vice President.—The Executive Vice President shall not be a medical man, nor a Fellow of the College, but shall, in fact, be a layman, preferably a lawyer. He shall exercise full and complete control over all its financial and business affairs and shall negotiate, supervise and sign any and all contracts and commitments made in its name or on its behalf. He shall exercise and carry out all such powers and duties, and shall observe all such directions and restrictions as the Board of Regents may, from time to time, confer or impose upon him, and shall, in turn, be responsible to and report only to it and to the Board of Directors. *He shall furnish a bond to the Corporation in such amount as the Board may require conditioned for the faithful performance of his trust.* As an executive officer of the College, he shall receive and be paid such annual compensation and salary as the Board of Regents may, from time to time, fix and determine.

(f) The Secretary.—The Secretary shall keep the minutes of all meetings of the College, the Board of Directors, and of the Board of Regents, and all the standing committees; shall see that all notices are duly given in accordance with the provisions of the By Laws; shall keep the records and the corporate seal and see that the seal is affixed to all documents requiring the same, and shall generally perform all duties incident to the office of Secretary, including such duties as may from time to time be assigned to him by the Board of Regents. The Secretary shall keep accurate reports of all members and their addresses with a record of attendance at meetings. He shall notify newly elected candidates of their election to membership. He shall submit the applications of candidates for membership to the Board of Regents, together with their qualifications for eligibility to membership. He shall receive and be paid such fixed compensation or salary annually as the Board of Regents may from time to time fix and determine.

(g) The Treasurer.—The Treasurer shall administer the funds of the College under the supervision of the Finance Committee, and he shall make such reports to the Finance Committee, the Board of Directors and the Board of Regents as may be required from time to time. He shall furnish a bond to the Corporation conditioned for the faithful performance of his trust.

(h) Counsel.—The man holding the office of Counsel shall be learned in the law and he shall give advice and counsel to the Board of Directors, the Board of Regents, and to the several officers and committees on all legal questions from time to time arising. He shall be appointed and retained by the Board of Regents for such periods of service as it may consider proper and he shall receive and be paid for his services such compensation as the Board of Regents may,from time to time, fix and determine.

(i) Consecutive Terms.—No officer shall hold office for two consecutive terms, except the Executive Vice President, the Secretary, and the Counsel.

(j) The Nominations of Officers.—The Nominating Committee shall be composed of five (5) members: The President, two (2) members of the Board of Regents each of whom has served at least two (2) years on the Board, and two (2) past Presidents, both Regents and past Presidents to be selected by the Board. *No member may serve on this committee for two consecutive years.* Not earlier than three (3) months, but not more than six (6) months after its selection the Nominating Committee shall pick one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those considered for selection, and all information contained in the membership records maintained in the Secretary's office as to any proposed selectees shall be seasonably supplied to the Committee for this purpose. The Nominating Committee shall report its selections to the Secretary's office and as soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed

(Continued on Page 630)

Letter to the Editor

This letter represents Dr. Weil's own opinion and is not to be construed to be the opinion of the Editor, the Editorial Board, or the Committee on Certification.

To the Editor,
ANNALS OF ALLERGY:

Those of us who are interested in the future of allergy and its definite establishment as a medical specialty in its own right are much agitated at present by the problem of certification. At this juncture, the solution found for a similar problem in the field of laboratory medicine should be of interest to your readers, because it offers an example of flexibility and fairness to men differing in training and experience without sacrificing high standards of proficiency.

As in the case of clinical medicine, new knowledge of high utility for diagnosis and therapeutic procedure is accumulating in the field of laboratory medicine. New techniques requiring highly specialized skill and highly specialized judgment in their proper evaluation have grown to the point where no longer can any single man cover adequately the whole field of medical laboratory sciences. Thus, the old general pathologist becomes more and more the expert in gross pathology and tissue work. Clinical chemistry, clinical microbiology (including immunology), hematology, and neuropathology are growing to specialties in their own right. In order to cover this situation adequately, the American Board of Pathology decided on an entirely new approach to the problem of certification. The old boards in pathologic anatomy and clinical pathology, singly or combined, are continued. In addition, special and independent boards were created for the four new specialties just enumerated. For those physicians already certified in clinical pathology and/or pathologic anatomy certification is offered after two years of supervised training in the special field of their choice and examination in that specialty. Physicians without diploma in pathology need five years of training in the area of one of the new specialty boards before they are admitted for examination. Thus, a man may, but need not, have certification in general pathology before being permitted examination in one of the newly recognized specialties. The over-all period of time required for training is approximately the same, whether he goes into the special field via training in general pathology or whether he prefers to spend all this time working in the special field of his choice.

The alternative pathways in preparing for certification in the specialties of laboratory medicine thus created seem to have much to recommend them. Evidently, there is a great similarity between the situation in the field of laboratory medicine and that in clinical medicine, where also new entities of special knowledge have gained and are gaining a status independent from the mother specialty of internal medicine. Thus, for instance, dermatology emerged in the past, and allergy is now struggling for recognition. Just as is the case of training in laboratory medicine, it can readily be seen that men with extensive experience in medicine—or, for that matter, in pediatrics—are well prepared to utilize to best advantage a further training in allergy. Thus time spent in the more general field and recognized by certification may justifiably be counted as part of training in allergy. However, the Board of Pathology has recognized that the minutiae of morbid pathology are no absolute requirement for a man planning to spend his life in, say, clinical microbiology. Similarly, it would seem evident that a good medical background, but not every detail of internal medicine (or pediatrics), is prerequisite for the making of a good allergist. It ought to

be remembered that many of the most important observations and techniques in allergy were developed by men primarily trained in such fields as otolaryngology or dermatology. The example of the solution found in laboratory medicine shows that there is really no need to close the door to men from other specialties—the future Hansels or Sulzbergers—if they should desire to make allergy the preponderant field of interest. Nor is there need to exclude men with good medical background and long and extensive experience in allergic diseases from acceptance to examination only because they do not possess the exact requirements needed for the Boards of Internal Medicine or Pediatrics. If the Board of Pathology found a way to circumvent the danger of erecting a Chinese wall around the new specialties, we ought to be able, in fairness and common sense, to build the new castle of our specialty board securely and safely without insisting that it have only one door of entrance.

One word, in closing, concerning another commendable feature in the new regulations of the Board of Pathology. For each of the new specialty boards, one year of training in a preclinical department of a university is accepted as a substitute for one year of training. A similar provision in the requirements for certification in allergy may be worthy of consideration. If properly adjusted to the particular needs of our field, it would serve to encourage the acquisition of desirable skills for future participation in investigative work on allergic diseases.

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BY LAW AMENDMENTS

(Continued from Page 628)

by ten (10) Fellows and sent to the office of the Secretary, provided said additional nominations are received in the office of the Secretary at least thirty (30) days prior to the next annual meeting. Nominations may also be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting.

(k) Vacancies.—(no change)

(l) Board of Directors.—The general management of the Corporation shall be vested in a Board of Directors composed of five members as hereinafter provided who shall in turn vest the details of management in the Board of Regents. The Board of Directors shall always be composed of the following officers: the retiring President, who shall be its Chairman, the incumbent President, who shall be its Vice Chairman, the President-Elect, the First Vice President and *the Treasurer*.

During the intervals between the meetings of the Board of Regents, the Board of Directors shall exercise all the powers of the Board of Regents in the management and direction of the business and conduct of the affairs of the College, except that it shall not have power to elect Fellows, to amend these By Laws, or to regulate fees or dues of Fellowship. It shall keep a record of its proceedings and shall, immediately after each meeting, report the same to the Board of Regents for approval at the next succeeding meeting of the Regents. The Board of Directors may fill vacancies occurring in its membership through death or resignation. Directors filling such vacancies shall continue on the Board until the expiration of the term in which the vacancy occurred, or until the next annual election of Officers.

ARTICLE VI. COMMITTEES

Section 2. Finance Committee

Delete the first paragraph and substitute in lieu thereof the following:

"The Finance Committee shall consist of three (3) members, each of whom shall be a retired chairman of the Board of Directors. Commencing in 1955 the retiring chairman of the Board shall always automatically become a member of said Committee to serve for a 3-year term during the last year of which he shall be its chairman. It shall be the duty and responsibility of this Committee to suggest ways and means whenever and wherever necessary of adding to the total income and revenues of the College."

(Wherever "Secretary-Treasurer" appears in the remainder of this section it will now read "Treasurer.")

THE AMERICAN COLLEGE OF ALLERGISTS

Twelfth Annual Instructional Course and Congress
Hotel New Yorker, New York, New York
April 15-20, 1956

The *Twelfth Annual Instructional Course,* April 15-17, 1956, with Dr. Morris A. Kaplan, Chairman, and Dr. M. Murray Peshkin, Co-Chairman, will be held at the Hotel New Yorker in New York. A tentative program has been set up, subject to change. Future issues of the ANNALS OF ALLERGY will contain important announcements and a complete program.

As the Instructional Course is arranged at the present time, Sunday morning, April 15, will be devoted to the basic sciences, and will include an introduction by Dr. M. Murray Peshkin, and lectures on Immunology as Applied to Allergy, Pathology of Allergy and Collagen Diseases, Physiology of Allergy, and Immunochemistry. The afternoon will be devoted to HAY FEVER and Non-seasonal Allergic Rhinitis, and will include discussions on botany and environmental factors. A treatment conference will be held, including such subjects as Specific Immunization, Nonspecific Therapy, Drug Therapy, Surgical Therapy, and Environmental Control. Sunday evening will be given over to a consideration of Office Procedures and a Practical Demonstration.

On Monday morning, April 16, the subject of BRONCHIAL ASTHMA will be covered. The Physiology of Respiration; Classification, Causes, and Complications of Bronchial Asthma; and Differential Diagnosis will be discussed, and a treatment conference will be held covering Specific Therapy, Drug Therapy, Corticosteroid Therapy, and Mechanical and Physical Aids. Between 12:00 and 2:00 there will be a continuation of Office Procedures and Practical Demonstration. Monday afternoon will be devoted to a discussion of ECZEMA AND OTHER ALLERGIC DERMATOSES, and will include such subjects as Pathology of Eczema, Infantile Eczema, Atopic Eczema in Adults, Contact Dermatitis, and Nonatopic Urticarial Dermatoses. A treatment conference will cover Steroid Therapy and Dietary Management. Monday evening will be devoted to an informal banquet where small groups will be able to discuss individual subjects with individual instructors.

The sessions on Tuesday morning, April 17, will cover SPECIAL PROBLEMS IN ALLERGY. The discussions will last for twenty or thirty minutes and will deal with The Importance of the Initial Interview, The Physician-Patient Relationship, Office Management of the Allergic Patient, Prophylaxis of Allergy in Childhood, Life Expectancy in Asthma, Institutional Management of Intractable Asthma in Childhood, and Management of Local and Constitutional Reactions. Between 12:00 and 2:00 Office Procedures and a Practical Demonstration will be conducted. MISCELLANEOUS ALLERGY will be the subject of the afternoon discussions, with special attention to Migraine and Allergic Headache, Urticaria, Allergy in Relation to Hematology, Physical Allergy, Allergy in Relation to the Cardiovascular System, and Psychosomatic Aspects of Allergy. Between 5:00 and 7:00 p.m. Office Procedures and a Practical Demonstration will again be conducted.

The General Scientific Session starts on Wednesday morning, April 18, and papers of fifteen or twenty minutes' length will be presented during the entire day and on Thursday morning, April 19. Between 12:00 and 2:00 the Office Procedures and Practical Demonstration will continue. The annual business meeting will be held on Thursday afternoon at 2:00, followed by the guest speaker who will be introduced by Dr. Giles Koelsche. From 6:00 to 7:30 on Thursday a cocktail party will be held, followed at 8:00 by the annual banquet.

All day Friday, April 20, will be given over to sectional meetings. From 9:00 to 12:00 the sections on Ophthalmic and Otorhinolaryngologic Allergy and on Dermatologic Allergy will meet, and from 12:00 to 2:00 the Ophthalmic and Otorhinolaryngologic Allergy Section will hold a luncheon meeting. From 2:00 to 5:00 p.m. the Sections on Psychosomatic and Pediatric Allergy will meet.

The deadline for papers for the Scientific Session is **December 1, 1955.** Papers should be submitted as soon as possible before that date to Dr. Ethan Allan Brown, 75 Bay State Road, Boston 15, Massachusetts.

News Items

ALLERGY FOUNDATION OF NORTHERN CALIFORNIA

Newly elected officers of the Allergy Foundation of Northern California, Inc., are: Chairman, Board of Governors, M. Coleman Harris, M.D., San Francisco; Vice Chairman, Grace Talbott, M.D., San Francisco; and Secretary-Treasurer, Albert Rowe, Jr., Oakland. All are Fellows of the American College of Allergists.

CHICAGO SOCIETY OF ALLERGY

The Chicago Society of Allergy has elected the following officers for the year 1955-1956:

President ..... Simon S. Rubin, M.D.
President-Elect ..... Helen C. Hayden, M.D.
Secretary-Treasurer ..... Norman J. Ehrlich, M.D.

FOURTH INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

Dr. C. Jiménez Díaz announces that the Fourth International Congress of Internal Medicine will be held in Madrid, Spain, September 19-23, 1956. Two main subjects will be discussed: "The Role of the Adrenals in the Pathogenesis and Evolution of Internal Diseases" and "Bronchial Asthma and Emphysema." A number of speakers will present both subjects, and individual presentations on these subjects and others will also be included. Additional information may be obtained from the secretaries, Drs. J. C. de Oya and J. Gimena, Hortaleza 90, Madrid, Spain.

PSORIASIS RESEARCH ASSOCIATION

The Psoriasis Research Association, a non-profit organization located at San Mateo, California, is attempting to raise funds to finance research on psoriasis, which afflicts an estimated four million persons in the United States. The association does not plan to conduct any research of its own, but rather to make grants of funds to the medical profession and research laboratories on the recommendation of its medical advisory board. Membership is open to all persons afflicted with this skin disease and to everyone interested in the work of the association. The annual membership fee is $5.00, with sponsoring memberships offered for $100 or more. Further information may be obtained from the Association at P. O. Box 513, San Mateo, California.

ELEVENTH INTERNATIONAL CONGRESS OF DERMATOLOGY

C. H. Floden, M.D., Secretary-General of the International Association of Dermatology, announces that the Eleventh International Congress of Dermatology will be held in Stockholm, Sweden, from July 31 to August 5, 1957. Preliminary information indicates that English, French, German, and Spanish will be the official languages of the Congress for both papers and discussion. The registration fee for full members is 175 sw. crowns and for associate members 100 sw. crowns, and the S. J. Travelbureau System, Vasagatan 1, Stockholm, has been appointed official agents for travel and accommodation. A preliminary program will be distributed to dermatologists by the end of this year. Further information may be obtained from the secretariat: Hudkliniken, Karolinska sjukhuset, Stockholm 60, Sweden.

POSTGRADUATE AND GRADUATE COURSES FOR PHYSICIANS

The Council on Medical Education and Hospitals of the American Medical Association has compiled a list of the graduate and postgraduate courses for physicians to be given from September 1, 1955, to August 31, 1956. This list is published in a special section of *The Journal of the American Medical Association* for July 23, 1955, beginning on page 1052. The approved postgraduate courses in allergy are listed as follows:

Institution	*Title of Course*	*Method of Instruction*	*Schedule of Course*	*Fee*
Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12, Ill.	Allergy & Related Conditions	Laboratory work Clinical case work	Sept. 21, 1955, 5 hours weekly for 10 weeks. Wed.	$125.00
Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12, Ill.	Allergy & Related Conditions	Laboratory work Clinical case work	March 21, 1956, 5 hours weekly for 10 weeks. Wed.	$125.00
Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12, Ill.	Asthma, Hay Fever & Allied Diseases	Laboratory work Clinical case work	Arranged. Full time. 4 weeks	$200.00
Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12, Ill.	Personal Course in Allergy	Laboratory work Clinical case work	Arranged. Full time. 6 months	$500.00
Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12, Ill.	Personal Course in Allergy	Laboratory work Clinical case work	Arranged. Full time. 4 weeks	$200.00
Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12, Ill.	Asthma, Hay Fever & Allied Diseases	Laboratory work Clinical case work	Arranged. Full time. 6 months	$500.00
State University of Iowa College of Medicine, Iowa City, Iowa	Allergic & Hormonal Management of Hay Fever & Asthma	Lecture or panel Demonstration	May 16, 1956. Full time. 1 day	$10.00
Chase Hotel, St. Louis, Missouri	American Academy of Allergy Postgraduate Course	Lecture or panel	Feb. 3, 1956. Full time. 3 days	None
Park Plaza Hotel, 220 N. Kingshighway, St. Louis, Missouri	Allergy in Relation to Otolaryngology	Laboratory work Small group discussion	May 30, 1956. Full time. 5 days	$150.00
New York University Post-Graduate Medical School, 550 First Ave., New York	Allergy	Laboratory work Clinical case work	Oct. 31, 1955. Full time. 3 weeks	$200.00
Beth-El Hospital, Brooklyn, New York	Allergy	Lecture or panel Demonstration	Oct., 1955, 2 hours weekly. 10 weeks	$30.00
New York University Post-Graduate Medical School, 550 First Ave., New York	Refresher Course in Allergic Conditions	Lecture or panel Demonstration	Mar. 12, 1956. Full time. 3 days	$50.00
New York University Post-Graduate Medical School, 550 First Ave., New York	Allergy	Lecture or panel Demonstration	April 13, 1956. 2 hours weekly for 8 weeks. Fridays	$40.00
Hotel New Yorker, New York	Graduate Instructional Course in Allergy, American College of Allergists	Laboratory work Clinical case work	Apr. 15, 1956. Full time, 3 days	$50.00
New York Medical College, Flower & Fifth Avenue Hospitals, New York	Allergy	Clinical case work Small group discussion	Anytime, 2½ hours weekly, 8 weeks, Tuesdays	$50.00
New York Polyclinic Medical School & Hospital, 345 W. 50th St., New York 19	Allergy	Laboratory work Clinical case work	Arranged	$50.00
Albert Einstein Medical Center, Northern Division, York & Tabor Roads, Philadelphia 41	Allergy	Clinical case work Lecture or panel	Fall, 1955. 3 hours weekly, 20 weeks, Thursdays	$75.00
Montefiore Hospital, Fifth Ave. at Darragh, Pittsburgh	Allergy	Laboratory work Clinical case work	May 7, 1956. Full time, 5 days	$50.00
University of Washington School of Medicine, Health Sciences Bldg., Seattle	Allergy	Clinical case work Small group discussion	Spring, 1956. Full time, to be arranged	Arranged

BOOK REVIEWS

PRACTICAL MEDICAL MYCOLOGY. By Edmund L. Keeney, A.B., M.D., F.A.C.P. Formerly in charge, Mycology Laboratory; Visiting Physician and Dispensary Physician (Allergy), The Johns Hopkins Hospital; Instructor in Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland. Edited by R. L. Pullen, M.D., Dean, University of Missouri School of Medicine, Columbia, Missouri. Springfield, Illinois: Charles C Thomas, 1955. 145 pages. Price $4.50.

No longer are diseases caused by fungi an unimportant and remote problem in medicine and public health. Vital statistics reports show that in the United States in 1949 fungus diseases accounted for 0.56 per cent of the total deaths from infectious diseases. Deaths attributed to fungous infections in 1949 exceeded the total of all deaths from infections by protozoa, rickettsiae, and helminths.

Therefore, this monograph in the American Lecture Series in Internal Medicine (Bannerstone Division) should be of considerable interest. It is compact and simply written in factual style for physicians, teachers, and students, making easy reading of a subject once considered highly technical.

The book contains sixteen chapters with references at the end of each. The author describes in separate chapters each disease of mycologic origin, giving historical background, geographic distribution, source of infection, incidence as related to age, sex, race, and occupation, symptomatology, physical and laboratory findings, roentgenograms, mycology, immunology, allergy, differential diagnosis, and treatment. Accompanying each chapter is a full page diagram showing in pictorial form the causative organism, geographic distribution, source of infection, clinical picture, laboratory findings, mycology, skin tests, and differential diagnosis. There are also chapters on fungus spores as allergens causing hay fever, asthma, and eczema, poisonous fungi as causes of mushroom poisoning, and ergotism.

This is a handy desk reference containing a great deal of information and practical suggestions readily obtained.

CASIMIR FUNK. Benjamin Harrow. 209 pages. Illustrations, bibliography and index. New York: Dodd Mead & Co., 1955. Price $4.00.

Casimir Funk is one of the greatest biochemists of our generation. As a result of his work with the causation of beri-beri in 1911, he in 1912 coined the word "Vitamine" to describe the earliest discovered accessory food factor. Having isolated thiamine, he proceeded to isolate nicotinic acid. He recognized, at an early date, that not only beri-beri, but also scurvy, pellagra, and rickets were deficiency diseases. Casimir Funk predicted that vitamins might be necessary for the manufacture of enzymes. Later he was able to devise a method of concentrating Vitamin A (and also D) the former useful in another deficiency disease, xerophthalmia. In 1929, he was able both to identify and separate the male hormone from urine, and also to show its quantity in the urine decreased with the onset of senility. Later, he proved a number of pituitary hormones to be present in the urine of pregnant females.

Subsequent work concerned itself with the detoxifying effect of liver extract on sulfanilamide toxicity; with the synthetic process of obtaining epinephrine and with a number of quantitative chemical procedures. This abbreviated list of Casimir Funk's accomplishments by no means do justice to his bibliography of some 150 papers dealing with physiologic and biochemical studies.

The contrast between the man and his biography is marked. Dr. Harrow is Dr. Funk's friend and collaborator, an able scientist in his own right. Friendship is rare-

ly a good basis for biography. The level of penetration is superficial and the story of Funk's life is itinerant and anecdotal. We are always told where he went, but rarely what he thought. We are told that Geneva "enchanted him" and that "situated on Lac Leman (the lake of Geneva) and dominated by Mont Blanc, this historic city made a deep impression on the youth of sixteen. He first dived deep into its language and thereby acquired fluency in French." Other figures of speech are equally lame. The author's language is always awkward, and he never misses an opportunity to use a cliché. People never originate or come from a city, they always "hail" from it. The city itself is always "a mecca." Scientists "pour out" research papers. One "steers clear of foods." Prospects always "look dim." In the South, "pellagra has an excellent feeding ground."

In medical literature, there have been a number of similar attempts by friends of the great pioneers. Few, indeed, have been successful because the writing of a biography is an art possessed by rare scientists. Unless a book can be read for pleasure, and because of its inherent literary qualities, it so often becomes a pedestrian list of places visited and a catalogue of papers written. In these two qualities, the book succeeds in being factual and accurate.—E.A.B.

ALLERGY COOKING. A Guide with Menus and Recipes. Marion L. Conrad. 380 pages, including index. New York: Thomas Y. Crowell Company, 1955. Price, $5.00.

This extremely useful volume gives round-the-clock assistance to food-sensitive people. Written by a home economist, herself a sufferer from food allergy, it is the fruit of experience gained in twenty years of working out allergy diets, and is a practical approach to the diet problems of food allergy sufferers. It will help physicians prepare diets for their allergy patients, complete with recipes, and will enable the patients better to follow their doctor's advice and at the same time help them enjoy appetizing and healthful meals.

Stress is placed on the importance of the doctor's role in determining and treating food allergies; therefore, this book does not supplant allergic management but rather supplements it. It is written on the assumption that the allergic patient knows which are the offending foods for him.

One of the common causes for failure in treating food allergy is that the patient does not know the elements which compose the food he eats. One section is devoted to "hidden pitfalls" which innocently cause so much trouble for the food-sensitive individual. He is urged to read the labels and to know the ingredients of gravy, salad dressings, ice cream, luncheon meats, etc. All types of food are discussed in detail, and their values and limitations are pointed out in relation to the various types of food allergies.

Special chapters deal with diets for babies, children, and the aged; diets for reducing and gaining weight; food for allergic patients on picnics, camping trips, parties, and when "eating out." Basic diets are given, as well as seven possible diet combinations. Over 600 recipes are included and entire menus are outlined; complete recipes are given for meat, poultry, and fish dishes; soups; salads; appetizers; vegetables; sauces; candies; desserts; and pickles. Sample charts for recording foods eaten and vitamin lists are also included.—V.E.S.

SYSTEMIC ASSOCIATIONS AND TREATMENT OF SKIN DISEASES. Kurt Wiener, M.D. 556 pages, 90 illus. St. Louis: C. V. Mosby Co., 1955. Price, $17.00.

This book is a companion to Wiener's previous book entitled "Skin Manifestations of Internal Disorders (Dermadromes)" published in 1947. The new book consists of two parts: "Systemic Associations of Skin Diseases," and "Systemic Treatment of

Skin Diseases." Although intended for the dermatologists, it should also be of great interest to the allergists, not only because it contains chapters on the various forms of eczema, urticaria, and pruritus, but also because of the chapters dealing with other skin diseases associated with hypersensitivity phenomena, such as the collagen diseases (lupus erythematosus, scleroderma, dermatomyositis), erythema multiforme, erythema nodosum, erythroderma, and especially the chapters on systemic treatment of skin diseases with steroids and other hormones, antibiotics, antihistaminic agents, vaccines, and unorthodox methods.

Dr. Wiener makes a unique contribution here, since he looks at skin diseases from a different angle. One may say that this book puts into large print and emphasizes those matters which in conventional textbooks on dermatology usually appear in small print. It contains a wealth of carefully sifted information not otherwise readily available to the general reader. It is well organized and well written; the individual chapters make stimulating reading. Its nearly 3,000 references document almost every statement in the book, and will be of great value for those who are interested in special aspects of the topics covered.

So ambitious an undertaking as Dr. Wiener's book, condensed in a handy volume of moderate size, cannot be expected to be without some shortcomings. There are some inequalities in the handling of the various topics. Lupus erythematosus is treated like a monograph, whereas the chapter on light allergies is barely more than a guide to better reading. The chapter on contact dermatitis is very short; no mention of the systemic id-like eruptions is made. In the chapter on urticaria one misses references to psychogenic factors. There is no chapter dealing with superficial fungus infections, their systemic manifestations, and the involvement of deeper tissues which occurs in infections with *trichophyton purpureum.*

However, these are minor points which do not detract from the intrinsic value of the book. This is not just a reference book for medical libraries; every dermatologist, and also every allergist who has more than a passing interest in dermatology, will enjoy owning this book, which lends itself to countless consultations.—S.E.

PROGRESS IN ALLERGY. Volume 4. Edited by Paul Kallós, Helsingborg 8⁰, Sweden. Cloth, 520 pp., with illustrations and tables. Boston: Little, Brown and Company, 1955. Price $20.00.

The fourth volume of "Progress in Allergy"possesses the same faults and virtues of its three predecessors. With the use of Taliaferro's table of Connective Tissue Cells Involved in Immune Reactions, Dr. Kallós discusses the broad basis of such reactions and their relationship to allergy. Dr. Bohrod writes a learned paper on the Histology of Allergic and Related Lesions. R. L. Mayer describes Group-sensitization to Compounds of Quinone Structures. Raffel gives a detailed Analysis of Delayed Hypersensitivities. The Biosynthesis of Adrenal Steroids is delineated by Pincus, and the Functional Inter-relationships between the Anterior Pituitary and the Adrenal Cortex by Engel. Dougherty postulates the Mechanisms of Action of Adrenal Cortical Hormones in Allergy. Respiratory Tract Allergy to Fungus Spores is described in full by Maunsell.

Each of these papers is undoubtedly erudite. The bibliographies are complete. Except, however, for occasional flashes of insight in the papers by Bohrod, Engel, Mayer and Pincus, the others are, in truth, rather dull. The reader feels that here are the experts who know "more and more about less and less." None of the papers are in any sense integrated with the others. The expert in each field will learn little that is new. For the non-expert, there is more here than he is very likely to want to know. As a reference book, this volume might find occasional use. It does not, however, represent "Progress in Allergy" and what it represents is certainly overpriced.

BOOK REVIEWS

DISTRIBUTION MAPS OF HAY FEVER PLANTS OF THE UNITED STATES. Tom Stemen, B.A., M.A., Oklahoma City, Okla., and Hugh Graham, B.S., M.S., Dallas, Texas. 173 maps, 4 x 6 inches, in file box. Price $22.50.

This compact durable file box contains 173 maps, each on a card 4 x 6 inches. A map is included for each important hay fever plant in the United States, showing its distribution, common name, scientific name, family name, habitat, and blooming period. These maps are the result of twenty-five years of field work on the part of the authors, who have collected and botanized all over the United States. An index divides the maps into grasses, weeds and shrubs, and trees which have been known to cause respiratory allergies in some part of the United States. The name of the hay fever pollen is listed in the upper left-hand corner of the card, and the area in which it occurs is indicated on a map of the United States by a series of dots, so that at a glance one can see whether a certain pollen occurs in a given area. In the lower left-hand corner of the card is printed the common name, the scientific name, the family name, habitat and season of bloom. The print is large and bold, so that a glance will reveal the desired information.

In the front of the file is an index, together with the code number of all the grasses, weeds and shrubs, and trees, as well as valuable suggestions for use of the maps. Since the names of some of the hay fever plants have been changed from time to time by American taxonomists, the old as well as the new name is used on the maps. The cultivated plants and farm crops are omitted, although they are believed to be the cause of much hay fever.

This set of maps may be obtained from Stemen Laboratories, P. O. Box 6306, Oklahoma City, Oklahoma, or Graham Laboratories, P. O. Box 12026, Dallas 25, Texas.—F.W.W.

AGEING—GENERAL ASPECTS. Vol. I of Ciba Foundation's Colloquia on Ageing. G. E. W. Wolstenholme and Margaret P. Cameron, editors for the Ciba Foundation. 255 pages, including index. Boston: Little, Brown and Company, 1955. Price, $6.75.

This volume represents the papers presented at the first of a series of conferences on the general subject of ageing, and covers the Ciba Symposium held in London, July 13-15, 1954, at which thirty-four participants from the United States, Switzerland, England, Belgium, Norway, Germany, India, and South Australia reported on various phases of gerontology. The conference was intended to be a general exploration of the subject and an evaluation of the present position and experiments on the processes directly or indirectly associated with tissue changes occuring with age.

Each chapter contains a paper presented on some aspect of the general subject, each is documented with references, and the discussion which followed presentation of the paper is included. After an opening discussion on the definition and measurement of senescence and general remarks on the pathologic basis of ageing, the mental and psychologic aspects of ageing were presented, as were the effects of ageing on respiratory function, on elastic tissue, calcium metabolism, 17-ketosteroid excretion, and incidence of certain vascular lesions; tissue transplantation technique and tissue preservation *in vitro* for study of ageing, the bearing of nutrition on ageing, and the too rapid maturation of children. The last chapter is a general discussion which sums up the papers presented and the discussion which had taken place.

Further symposia will be held in this colloquia on ageing, and the Ciba Foundation is to be congratulated on having initiated discussion of this subject which is of ever-growing interest and implications.—V.E.S.

COUGH SYNCOPE. Vincent J. Derbes, M.D., Tulane University School of Medicine, and Andrew Kerr, Jr., M.D., Louisiana State University School of Medicine, New Orleans, Louisiana. 182 pages. Springfield, Illinois: Charles C Thomas, 1955. Price $4.75.

Cough syncope, or fainting following cough, known also as laryngeal vertigo, cough, syndrome, tussive or tussigenic syncope and a variety of other names, was first noted in 1876 by Charcot and it evinced much interest on the continent. Until very recently the bulk of the literature on this subject was contained in foreign writings, with almost no attention given the subject by American observers.

The authors, in this little volume in the Bannerstone Division of American Lectures in Internal Medicine, a part of the American Lecture Series, present twenty-five cases coming under their personal observations, plus ten additional cases made available to them by colleagues, and note 255 reported instances in the literature. Various theories explaining the syndrome are discussed, especially the neurogenic and circulatory, the authors leaning toward the latter theory. All phases of the symptom-complex are covered: symptomatology, history, related conditions (epilepsy, narcolepsy-cataplexy, laryngeal crises of tabes dorsalis, and voluntary death by breath holding), physiologic mechanisms, prognosis, treatment, and medicolegal aspects. Through the authors' review of the literature and personal observation of their patients, they have developed a definite clinical picture of this syndrome: its almost exclusive occurrence in males, the usual presence of mild emphysema and asthma; predilection for obese individuals; definite relationship to excessive smoking; frequent occurrence while eating, drinking, or laughing; increased incidence in middle age; and occurrence following a dry, unproductive cough. Treatment is difficult, at present mainly consisting of removal of the cause of the cough or suppression of the stimuli for coughing.

A bibliography of over 350 references is included, as well as a complete index. This subject should be of concern to general practitioners, internists, neurologists, and otolaryngologists, all of whom are likely to encounter the problems involved in cough syncope. This volume summarizes present knowledge of the subject and should serve as a handy reference.—V.E.S.

NEW INSULIN SYRINGE FOR THE DIABETIC BLIND

National Surgical Supply Co., 458 Broadway, an affiliate of Allergists Supply Company, New York, has recently placed on the market a 1 cc insulin syringe with dose gauge and luer needle lock attacked, graduated in 40 and 80 units, designed especially for the diabetic blind and for persons with impaired vision. The gauge consists of a slatted strip anchored to the plunger, and a stop fastened to the strip, which by means of a screw is directed through the slot and against the top of the barrel. By withdrawing the plunger to the required dose, and tightening the screw, the patient will continue to receive the same dosage until the physician or nurse resets the gauge. The gauge is adaptable to any short type 1 cc insulin syringe, and the needle lock is an obvious improvement over the glass luer tip. Stainless steel needles are available in every length and gauge. The syringes sell for $5.00, with reductions for quantity orders.